EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 December 2025
EMA/10052/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MYQORZO

International non-proprietary name: aficamten

Procedure No. EMEA/H/C/006228/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Administrative information

Name of the medicinal product:	MYQORZO
Applicant:	Cytokinetics (Ireland) Limited 45 Mespil Road Dublin 4 D04 W2F1IRELAND
Active substance:	aficamten
International Non-proprietary Name/Common Name:	aficamten
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication:	MYQORZO is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	5 mg, 10 mg, 15 mg and 20 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/alu)
Package size(s):	28 tablets

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List of abbreviations

Abbreviation	Explanation
ACC	American College of Cardiology
ADR	adverse drug reaction
AE	adverse events
AESI	adverse events of special interest
AHA	American Heart Association
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration-time curve time from 0 to infinity
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
BCS	Biopharmaceutics Classification System
BSV	between-subject variability
%CV	percent coefficient of variation
$C_{avg,24}$	average concentration over the 24-hour dosing interval
CI	confidence interval
C_{max}	maximum plasma concentration
CMI	cardiac myosin inhibitors
CMQ	customized MedDRA Query
COVID-19	coronavirus disease 2019
CPET	cardiopulmonary exercise testing
CSR	clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
DDI	drug-drug interaction
EAIRs	exposure-adjusted incidence rates
ECG	Electrocardiogram
EOP2	End of Phase 2
ESC	European College of Cardiology

Abbreviation	Explanation
FDA	Food and Drug Administration
HCM	hypertrophic cardiomyopathy
hERG	human ether-à-go-go-related gene
hs-cTnI	high-sensitivity cardiac troponin I
ISS	integrated Summary of Safety
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire – Overall Summary Score
LS	least squares
LAVI	left atrial volume index
LV	left ventricular
LVEF	left ventricular ejection fraction
LVMI	left ventricular mass index
LVOT	left ventricular outflow tract
LVOT-G	left ventricular outflow tract gradient
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
nHCM	nonobstructive hypertrophic cardiomyopathy
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PBPK	physiologically based pharmacokinetics
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
pVO_2	peak oxygen uptake
QD	once daily
QTc	corrected QT
REMS	Risk Evaluation and Mitigation Strategy

Abbreviation	Explanation
RER	respiratory exchange ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMQ	standard MedDRA Query
SRT	septal reduction therapy
$t_{½}$	apparent plasma terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
US	United States
USPI	US Prescribing Information
w/w	weight for weight

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Cytokinetics (Ireland) Limited submitted on 20 November 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Myqorzo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 10 November 2022.

The applicant applied for the following indication: MYQORZO is indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0123/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0123/2024 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance aficamten contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific Advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
24 June 2021	EMA/SA/0000058861	Clemens Mittmann, Silvijus Abramavicius
20 July 2023	EMA/SA/0000139645	Ivana Haunerova, Adriana Ammassari

The Scientific advice pertained to the following quality and clinical aspects:

EMA/SA/0000058861 - Clinical development

- The design of the proposed phase 3 trial (CY 6031), the primary/secondary endpoints and analysis methods, the target patient population and proposed eligibility criteria, dosing and blinding strategy.
- The adequacy of the proposed safety database and of a single phase 3 trial for MAA.

EMA/SA/0000139645 - Quality development

- Adequacy of the proposed designation of starting materials for commercial manufacture of the drug substance; the overall control strategy for the impurities in the drug substance; the proposed stability programme; the proposed commercial dissolution method.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Antonio Gomez-Outes

The application was received by the EMA on	20 November 2024
The procedure started on	27 December 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 March 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 April 2025
A GCP inspection at 3 sites: one clinical site in China, one clinical site in Spain and at the sponsor site in USA between 22 April 2025 and 28 May 2025. The outcome of the inspection carried out was issued on 15 July 2025.	15 July 2025
The applicant submitted the responses to the CHMP consolidated List of	13 August 2025

Questions on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 September 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	16 October 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to MYQORZO on	11 December 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	11 December 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Obstructive hypertrophic cardiomyopathy (oHCM) is a genetic cardiac disorder characterized by thickened heart muscle, primarily affecting the left ventricle, and causing obstruction of blood flow during contraction. This obstruction, often at the level of the left ventricular outflow tract, results in symptoms such as chest pain, shortness of breath, fainting, and in severe cases, sudden cardiac death. The condition is commonly linked to mutations in sarcomere protein genes and is managed through lifestyle changes, medications, or invasive procedures like septal reduction therapy.

2.1.2. Epidemiology

In the recent DARWIN study conducted in six EU countries (https://catalogues.ema.europa.eu/node/4331/administrative-details) the HCM prevalence increased over time across all databases, reaching values ranging from 0.043% (95%CI: 0.041–0.046) in UK CPRD-GOLD in 2023 to 0.237% (95%CI: 0.233–0.241) in SIDIAP in 2022. The prevalence trend for oHCM mirrored that of HCM but values remained consistently lower, ranging from 0.027% (95%CI: 0.025–0.029) in CPRD-GOLD to 0.069% (95%CI: 0.067–0.072) in NLHR in 2023.

Approximately 70% of patients with phenotypic HCM will demonstrate an element of LVOT obstruction (Maron, M. S. 2006).

2.1.3. Biologic features

MYH7 and MYBPC3, encoding β-myosin heavy chain and myosin-binding protein C, respectively, are the two most common genes involved, together accounting for approximately 50% of the HCM families (Elliott 2014). Mechanistically, mutations in HCM appear to increase the net power generation in the sarcomere in vitro (Chuan 2012; Sommese 2013; Spudich 2016; Toepfer 2019). The findings in these studies are consistent with the underlying myocardial pathophysiology of the LV in patients with HCM being hypercontractile with diminished compliance (Wilson 1967). Histologic features include myofibrillar disarray, myocyte hypertrophy and interstitial fibrosis.

The mechanisms for developing obstruction involve a complex interplay between alterations in ventricular flow between asymmetric septal hypertrophy and the mitral valve leaflets. 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). By nature, oHCM is a dynamic condition with variable systolic gradients. In the setting of reduced afterload or reduced preload, symptoms change depending on the gradient and often worsen during exertion

2.1.4. Clinical presentation, diagnosis

Clinically, HCM is characterized by left ventricular (LV) hypertrophy unexplained by loading conditions and a nondilated LV with preserved or increased ejection fraction (Gersh 2011). Imaging studies of patients with HCM show hypertrophied LV walls, enhanced ventricular contractility, normal end-diastolic LV volume, reduced end-systolic volume, impaired diastolic compliance and often left atrial enlargement (Marian 2017). Additional clinical manifestations of HCM include an elevated risk for ventricular fibrillation and sudden cardiac death; heart failure syndrome due to diastolic dysfunction; chest pain due to microvascular ischemia; palpitations and stroke due to atrial fibrillation; syncope and presyncope due to either ventricular arrhythmias or an abnormal blood pressure response to exercise; and, in a minority of patients, progression to systolic heart failure.

2.1.5. Management

Current management strategies for oHCM have resulted in the majority of patients achieving normal or near-normal longevity and improved morbidity; however, there has been little progress with the development of novel pharmacotherapies. Current medical treatment consists of beta-blockers, verapamil, diltiazem and disopyramide as recommended in the 2014 European Society of Cardiology and in the 2011 American College of Cardiology Foundation / American Heart Association guidelines for the diagnosis and management of HCM. Cardiac myosin inhibitors (CMIs) constitute a new class of drugs, that directly targets the underlying pathophysiology of HCM. The first-in-class CMI is mavacamten, which is approved for the treatment of symptomatic oHCM in the year 2023, and has been shown to improve symptoms and exercise capacity in patients with oHCM. For patients with advanced symptomatic disease unresponsive to medications, septal reduction therapies (surgical myectomy or percutaneous alcohol ablation of the septum) can provide effective LVOT-G reduction (Elliott 2014; Gersh 2011; Ponikowski 2016). A subgroup of patients, who have been resuscitated from sudden cardiac death or who are at risk of sudden cardiac death, may undergo placement of an implantable cardioverter defibrillator (ICD) (Kristensen 2014). For those patients with HCM with end-stage disease who have both significant systolic impairment and diastolic dysfunction, cardiac transplantation may be the only treatment option (Gersh 2011). Disease-related mortality is most often attributable to sudden cardiac death, heart failure, and embolic stroke.

2.2. About the product

Aficamten is a small molecule, cardiac myosin inhibitor designed to reduce the hypercontractility that underlies the pathophysiology of HCM in the cardiac sarcomere. The reduction in cardiac contractile force is expected to alleviate LVOT obstruction in patients with oHCM by counteracting the excessive thickening of the left ventricular wall of the outflow tract. LVOT obstruction is a primary cause of morbidity in the majority of patients with symptomatic oHCM.

Direct inhibition of cardiac myosin to relieve hypercontractility and LVOT obstruction in patients with HCM is a targeted pharmacologic approach intended to improve functional capacity and symptoms. Reduction of LVOT obstruction increases cardiac output, decreases intraventricular systolic pressure, and may also prevent progression of hypertrophy and fibrosis, which could translate into additional longer term clinical benefit for patients with oHCM.

The proposed indication for aficamten in the EU was as follows: MyQorzo is indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

The approved by the CHMP indication for aficamten is: MYQORZO is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).

The approved posology and method of administration is:

Treatment should be initiated under the supervision of a physician experienced in the management of patients with cardiomyopathy.

Before treatment initiation, left ventricular ejection fraction (LVEF) should be assessed by echocardiography (see section 4.4). Initiation or up-titration of MYQORZO in patients with LVEF < 55% is not recommended. Regular LVEF and Valsalva left ventricular outflow tract gradient (LVOT-G) assessment should be performed during titration to achieve an appropriate target Valsalva LVOT-G, while maintaining LVEF ≥ 50%.

Posology

The dose range is 5 mg to 20 mg (either 5 mg, 10 mg, 15 mg, or 20 mg). The recommended starting dose is 5 mg orally once daily. A starting dose of 10 mg should be considered for patients with LVOT-G ≥ 100 mmHg. 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 Table 1.

Table 1: Dose adjustment of aficamten

LVEF	Valsalva LVOT-G	Dose adjustment
≥ 55%	≥ 30 mmHg	Increase dose by 5 mg (up to the maximum dose of 20 mg once daily)
≥ 55%	< 30 mmHg	Maintain dose
< 55% and ≥ 50%	Any	Maintain dose
< 50% and ≥ 40%	Any	Decrease dose by 5 mg[1] Interrupt treatment for 7 days for 5 mg dose

< 40%	Any	Interrupt treatment for at least 7 days.

[1] Dose decrease as follows: from 20 mg to 15 mg; from 15 mg to 10 mg; from 10 mg to 5 mg

An echocardiographic assessment should be performed 2 to 8 weeks after initiation of treatment, any dose adjustment, or treatment interruption. 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% (see Table 1).

After the maintenance dose has been established, LVEF and Valsalva LVOT-G should be assessed every 6 months, or every 3 months in patients with LVEF ≥ 50% to < 55%. Consider monitoring LVEF and adjust dose per Table 1, as needed, in patients with intercurrent illness (e.g. severe infection or COVID-19), new arrhythmia (e.g. new or uncontrolled atrial fibrillation or other uncontrolled tachyarrhythmia) or any other conditions that may impair systolic function. Dose increases are not recommended until intercurrent illness or new arrythmia has resolved or stabilised.

Discontinuation of aficamten may result in recurrence of HCM symptoms. Gradual dose reduction may attenuate the rate of symptom recurrence following treatment discontinuation (see section 4.4).

Dose modification with concomitant medicinal products

- Concomitant use with moderate CYP2C9 inhibitors that are also moderate-to-strong inhibitors of CYP2D6 or CYP3A e.g. more than a single dose of fluconazole or strong inducers e.g. rifampicin is contraindicated (see section 4.3).
- Concomitant use of aficamten with strong CYP2C9 inhibitors should be avoided. If coadministration cannot be avoided, the dose of aficamten should be reduced to 5 mg and LVEF and LVOT-G assessed every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).
- The recommended starting dose is 5 mg once daily in patients who are on stable therapy with a weak CYP2C9 inhibitor that is also a moderate-to-strong CYP2D6 or CYP3A inhibitor (e.g. voriconazole, fluvoxamine). The maintenance dose of aficamten should not exceed 15 mg.
- For patients who initiate a weak CYP2C9 inhibitor that is also a moderate-to-strong CYP2D6 or CYP3A inhibitor, the dose of MYQORZO should be reduced to 5 mg if they are currently receiving 15 mg or 20 mg. Concomitant use should be avoided if patients are currently receiving MYQORZO 5 mg or 10 mg. The maintenance dose of aficamten should not exceed 15 mg. LVEF and LVOT-G should be assessed every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).
- For patients who intend to discontinue a moderate-to-strong CYP2C9 or CYP3A inducer (e.g. carbamazepine), the dose should be reduced (from 20 mg to 10 mg; from 15 mg to 5 mg; from 10 mg to 5 mg) according to Table 2 (see also section 4.5). For patients currently receiving 5 mg, maintain the 5 mg dose. LVEF and LVOT-G should be assessed after inducer discontinuation. Assessment of LVEF and LVOT-G and dose titration according to Table 1 is recommended.

Table 2: Dose modification of aficamten with concomitant medicinal products

<table>
<tr><th>Concomitant medicinal product</th><th>Initiating aficamten while on stable medicinal product treatment</th><th>Initiating medicinal product while on stable aficamten treatment</th><th>Discontinuing medicinal product while on stable aficamten treatment</th></tr>
<tr><td colspan="4">Inhibitors</td></tr>
<tr><td>Any strong CYP2C9 inhibitor (e.g. sulfaphenazole)</td><td colspan="3">Avoid concomitant administration. If coadministration cannot be avoided, reduce the dose of aficamten to 5 mg and assess LVEF and LVOT-G every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).</td></tr>
<tr><td>Any moderate CYP2C9, and moderate-to-strong CYP2D6 or CYP3A, inhibitor (e.g. fluconazole, adagrasib)</td><td colspan="3">Coadministration is contraindicated for more than a single dose of fluconazole (see section 4.3).

Adagrasib coadministration is contraindicated (see section 4.3).</td></tr>
<tr><td rowspan="3">Any weak CYP2C9 and moderate-to-strong CYP2D6 or CYP3A inhibitor (e.g. fluvoxamine, voriconazole)</td><td>Initiate aficamten at the recommended starting dose of 5 mg once daily.</td><td>Reduce the dose of aficamten from 20 mg to 5 mg, from 15 mg to 5 mg.

Avoid if on 10 mg or 5 mg aficamten (see section 4.5).</td><td rowspan="2">No dose adjustment needed.</td></tr>
<tr><td colspan="2">The maintenance dose of aficamten should not exceed 15 mg. LVEF and LVOT-G should be assessed every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).</td></tr>
<tr><td colspan="3">Assess LVEF and LVOT-G, and dose titrate/monitor according to Table 1.</td></tr>
<tr><td colspan="4">Inducers</td></tr>
<tr><td>Moderate CYP2C9 and strong CYP3A inducer (e.g. rifampicin)</td><td colspan="3">Concomitant use with rifampicin is contraindicated (see section 4.3).</td></tr>
<tr><td rowspan="2">Any moderate-to-strong CYP2C9 or CYP3A inducer (e.g. carbamazepine)</td><td>Initiate aficamten at the recommended starting dose of 5 mg once daily.</td><td>No dose adjustment needed.</td><td>Reduce dose of aficamten from 20 mg to 10 mg, from 15 mg to 5 mg, from 10 mg to 5 mg. No dose adjustment is required for patients currently receiving 5 mg of aficamten (see section 4.5).</td></tr>
<tr><td colspan="3">Assess LVEF and LVOT-G, and dose titrate/monitor according to Table 1.</td></tr>
</table>

Missed doses
If a dose is missed, it should be taken as soon as possible on the same day. The next scheduled dose should be taken at the usual time the following day. Two doses should not be taken the same day.

Elderly
No dose adjustment is required for patients aged 65 years and older.

Renal impairment
No dose adjustment to the standard recommended dose and titration schedule is required for patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min) to moderate (eGFR 30 to 59 mL/min) renal impairment. No dose recommendation can be made for patients with severe (eGFR < 30 mL/min) renal impairment because aficamten has not been studied in patients with severe renal impairment.

Hepatic impairment
No dose adjustment to the standard recommended dose and titration schedule is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. No dose recommendation can be made for patients with severe hepatic impairment (Child-Pugh class C) because aficamten has not been studied in patients with severe hepatic impairment.

Paediatric population
The safety and efficacy of aficamten in children and adolescents below 18 years have not been established. No data are available.

Method of administration
For oral use. Treatment should be taken once daily with or without meals. The tablet should be swallowed whole with water and not split, crushed, or chewed as these methods have not been studied.

2.3. Type of Application and aspects on development

2.3.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.3.2. The development programme/compliance with guidance/scientific advice

An overview of compliance with the EMA scientific advice (SA) is shown in Table 2.

Table 1. Compliance with EMA scientific advice

Questions	Responses	Compliance
Does the CHMP agree with the proposed primary	Exercise testing can be acceptable as the primary endpoint, but meaningful data on hard clinical endpoints are additionally needed. And a negative impact on cardiovascular events should be excluded with reasonable confidence	Partially compliant

endpoint and analysis method?		
Does the CHMP agree with the proposed secondary endpoints and analysis methods?	The KCCQ clinical summary score is an acceptable means to assess quality of life of heart failure patients. A 10-point decline in KCCQ scores is considered clinically relevant and has important diagnostic significance. NYHA class, LVOT-G decrease and CPET parameters are adequate secondary endpoint. Preference to also measure after 10 weeks, rather than only 24 weeks.	Compliant
Does the CHMP agree with the target patient population and proposed eligibility criteria?	The Applicant should further justify the exclusion of patients with documented paroxysmal atrial fibrillation during screening or with paroxysmal/permanent atrial fibrillation requiring rhythm restoring treatment ≤6 months prior to screening. Inclusion of patients only with a respiratory exchange ratio (RER) ≥1.05 and pVO2 <80% predicted on the screening CPET should be justified.	Not compliant
Does the CHMP agree with proposed individualized dosing strategy of titration	Generally endorsed. It should be ensured that the 2-week up-titration intervals are long enough to reach a new steady state. Inclusion of a Pop PK/PD analysis in the pivotal trial is recommended. The Applicant should define the rescue therapy required in case of overdosing or cardiovascular events.	@PK Compliant (last point)
Does the CHMP agree that the proposed packaging configuration and the use of dummy titration?	The Applicant is requested to clarify the dummy strategy, because it is currently unclear how it is possible to randomly select patients from the placebo group without unblinding the study. As a partial solution to achieve at least some blinding across dose levels, the tablets could be put into equally sized gelatin capsules that are sufficiently large to contain each of the dose levels.	Not compliant
Does the CHMP agree that the proposed single phase 3 study could be the basis for approval?	The Applicant plans to test the primary endpoint with an alpha of 0.05. Recommended to use lower alpha. In addition, the study duration should be extended to at least 1 year, and the size of the trial population should be considerably increased in order to meet this requirement. Moreover, pending assessment of the MAA, further confirmation with morbidity and mortality data after registration may be required.	Not compliant
Does the CHMP agree that the safety database will be sufficient to support a marketing application?	It is recommended to extend the study duration to at least one year or longer and to include an additional endpoint addressing cardiovascular safety. The ICH E1 guideline mentioned above states that "100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base." Pending assessment of the MAA, further confirmation of safety after registration may be required (e.g., post-approval commitments, additional monitoring status)	Not compliant

2.3.3. General comments on compliance with GMP, GLP, GCP

GMP compliance could be confirmed for all proposed sites.

All pivotal non-clinical studies were GLP compliant and deviations or amendments were appropriately recorded.

The applicant claims that the pivotal clinical study CY 6031 was conducted in compliance with good clinical practice and was conducted under the EU Clinical Trial Directive (2001/20/EC). A routine GCP inspection has been adopted.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 5 mg, 10 mg, 15 mg, or 20 mg of aficamten as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (E460(i)), mannitol (E421), croscarmellose sodium (E468), hydroxypropylcellulose (E463), sodium laurilsulfate, and magnesium stearate (E470b).

Film coating: macrogol poly(vinyl alcohol) grafted copolymer (E1209), talc (E553b), titanium dioxide (E171), glycerol mono and dicaprylocaprate (E471), poly(vinyl alcohol) (E1203), indigo carmine aluminium lake (E132), and carmine (E120).

The product is available in polyvinylchloride (PVC)/aluminium foil blisters as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of aficamten is *N*-[(R)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-1-indanyl]-1-methyl-4-pyrazolecarboxamide corresponding to the molecular formula $C_{18}H_{19}N_5O_2$. It has a relative molecular mass of 337.38 Daand the following structure:

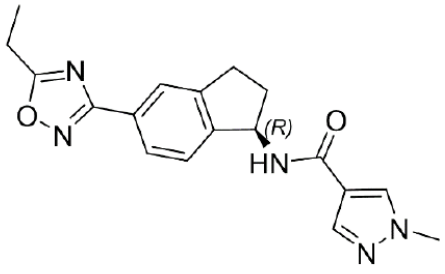


Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of single crystal x-ray structure determination, NMR spectroscopy, mass spectrometry (MS), infrared spectroscopy (IR),

ultraviolet spectroscopy (UV), and elemental analysis. The solid-state properties of the active substance were measured by XRPD analysis.

The active substance is a non-hygroscopic powder, practically insoluble in aqueous media. The solubility of aficamten in various media, including those with pH values ranging from 2 – 9, as well as in water, simulated gastric fluid (SGF), and fasted state simulated intestinal fluid (FaSSIF). In addition, aficamten is slightly soluble in common organic solvents.

The active substance exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation.

Polymorphism has been observed for the active substance. Polymorphic forms of aficamten have been identified and confirmed by a test for polymorphic form by XRD in the active substance specification. The XRD method is specific.

Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site. Evidence of GMP compliance has been provided.

The active substance is synthesized in 3 main steps using well defined starting materials with acceptable specifications.

The starting materials are adequately controlled by their specifications. The specifications of intermediates are sufficient to ensure the consistent production of active substance of the intended quality.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of active substances.

Potential organic impurities, residual solvents, elemental impurities and nitrosamine impurities have been adequately discussed. For the mutagenic impurities, the QSAR study reports, required to justify the classification of potentially mutagenic impurities according to IC M7, were not provided during evaluation. Therefore, the CHMP requested this information to be provided as major objection (MO). In response to a MO related to potential mutagenic impurities (PMI), the applicant demonstrated that all relevant impurities are considered non-mutagenic, thereby justifying the proposed control strategy.

The development of the commercial route of synthesis has been described including its evolution over time. The provided information is considered sufficient.

The active substance primary packaging complies with Commission Regulation (EU) 10/2011.

Specification

The active substance specification includes tests for: appearance (visual), identity (HPLC, UV), assay (HPLC), impurities (HPLC, UPLC), chiral purity (chiral HPLC), residual solvents (GC), water content (Ph. Eur.), residue on ignition (Ph. Eur.), elemental impurities (Ph. Eur.), and particle size (Ph. Eur.), polymorph form (XRD).

Impurities were qualified and appropriate specifications have been set according to ICH Q3A.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

The omission of a microbial enumeration test in the active substance specification has been sufficiently justified. This is supported by confirmatory testing of multiple batches. In addition, microbial enumeration is tested in finished product.

Batch analytical data has been provided on multiple batches at different stages of the process/product development. The results demonstrated that the manufacturing process results in consistent product quality.

Batch analyses data of the active substance are provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from multiple batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, assay, impurities, water content and polymorphic form. The analytical methods used were the same as for release and were stability indicating.

Under long term and accelerated stability conditions, all batches tested met the acceptance criteria listed in each study. None of the batches showed any change for any attributes tested.

Photostability testing following the ICH guideline Q1B was performed. Both the dark control and light-exposed samples met acceptance criteria indicating that aficamten is not susceptible to photodegradation.

Forced degradation was conducted using various stressed conditions including acid, alkaline, oxidation, heat, and photolysis. The analytical methods used for assay and impurities testing were demonstrated to be stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months without specific storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished products are film-coated tablets containing either 5, 10, 15 or 20 mg of aficamten. The different tablet strengths are described as follows:

5 mg: Purple, round tablet debossed with "5" on one side and "CK" on the other side. Tablet size of approximately 4.84 mm in diameter.

10 mg: Purple, triangular tablet debossed with "10" on one side and "CK" on the other side. Tablet size of approximately 6.73 mm x 6.99 mm.

15 mg: Purple, pentagonal tablet debossed with "15" on one side and "CK" on the other side. Tablet size of approximately 7.33 mm x 7.37 mm.

20 mg: Purple, oval tablet debossed with "20" on one side and "CK" on the other side. Tablet size of approximately 5.46 mm x 10.29 mm.

For the development of the finished product, elements of QbD were applied. A quality target product profile (QTPP) was defined, and risk assessment was used to identify Critical Quality Attributes (CQAs) of the finished product.

Active substance attributes with a potential impact on finished product performance and manufacturability have been discussed.

Excipients were selected from common excipient combinations, utilizing prior knowledge of the material properties for the selected manufacturing unit operation process and the quality target product profile. All excipients were shown to be compatible with the active substance.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards except the colourants which comply with in house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in section 2.4.1 of this report.

Clinical studies were performed using only the 5 mg strength. For the higher doses used in the clinical studies (10, 15 and 20 mg) multiples of these 5 mg tablets were used. The 5 mg batches used are representative of the commercial 5 mg product. These batches were manufactured according to the finalized composition and manufacturing process, but with a white coating instead of the commercial purple coating. The coating is non-functional, and the change does not impact the finished product performance. This was sufficiently confirmed by the provided comparative dissolution data. However, the CHMP considered that the biowaiver for the 10, 15 and 20 mg product strengths was not adequately justified. The initial comparative multi-media dissolution data supporting the bridge between the 5 mg clinical batches and the additional commercial strengths did not meet all the requirements of the Guideline on the investigation of bioequivalence for a waiver for additional strengths resulting in a MO: dissolution should be demonstrated between the 5 mg product and the 10, 15 and 20 mg products without the use of surfactant. Additionally, a non-standard paddle speed was used for the paddle apparatus. In response, the applicant provided data from comparative dissolution studies in line with the recommendations. Dissolution profiles were similar (all calculated f_2 values are above 50) between the 5 mg clinical tablet and the 5, 10, 15 and 20 mg commercial tablets. Therefore, the issue was considered resolved and the biowaiver of strengths is considered acceptable.

The manufacturing process development has been described in sufficient detail.The primary packaging is polyvinylchloride (PVC)/aluminium foil blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process consists of seven main steps: dispensing, wet granulation and milling, drying, dry milling, blending and lubrication, compression, coating, and blister packaging. The process is considered to be a standard manufacturing process.

Sufficient information on the in-process controls and sampling frequencies has been provided. The acceptance criteria are in line with the development data and data obtained for the primary stability batches and with general Ph. Eur. requirements.

No process validation data have been provided which is acceptable as the process is standard. Process validation will be conducted prior to commercial distribution.

The process validation scheme and bracketing approach are considered acceptable.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identity (HPLC, UV), assay (HPLC), impurities (HPLC), water content (Ph. Eur.), uniformity of dosage units by content uniformity (HPLC), dissolution (HPLC), microbial enumeration tests (Ph. Eur.), and tests for specified organisms (Ph. Eur.).

No degradation products have been observed to date in the finished product at or above the ICH Q3B identification threshold of ≥ 0.2% based on the maximum daily dose. Long-term and accelerated stability data available for primary stability batches and supportive stability batches showed little change with little variability observed for impurities.

The initially proposed dissolution limit was not considered acceptable by CHMP resulting in an MO. The dissolution limit was tightened in line with batches used in pivotal clinical studies and the response was considered satisfactory.

A risk assessment was conducted for potential elemental impurities from the excipients and finished product using the ICH Q3D Option 2b approach. It was demonstrated that the total elemental impurities from the excipients and finished product are negligible and well below the ICH Q3D control threshold (< 30% of permitted daily exposure). Potential impurities from the finished product manufacturing process, water used, and packaging components were also assessed. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was provided. The applicant had identified potential nitrosamine impurities which could form from the residual solvents used in the active substance manufacturing process. The analytical methods used for confirmatory testing had not been validated and a potential nitrosamine impurity had not been considered, resulting in a MO. In response, the applicant provided the requested validation data and also confirmatory testing data. None of the tested nitrosamines were detected above 10% of their acceptable intake (AI) limit. Therefore, it was accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product, and the major objection was considered resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data have been provided on batches of 5, 10, 15 and 20 mg products. The batches were stored at 25°C/60% RH (up to months), and 40°C/75% RH (up to 6 months). The batches were

packed in PVC-Al blisters. Stability studies and conditions were performed according to the ICH guidelines.

The following parameters were investigated: appearance, assay, impurities, water content, dissolution and microbiological quality (only long-term). All tested parameters were compliant with the specification.

In addition, the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It was concluded that the finished product is not sensitive to light.

A thermal cycling stability study of the finished product in blisters for all strengths was conducted and there was no change with respect to all stability-indicating attributes.

Forced degradation was conducted in all strengths using various stressed conditions including acid, base, oxidation, heat, and photolysis. Little degradation was observed under the other conditions.

Based on available stability data, the proposed shelf-life of 30 months when stored below 30 °C as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. Four MOs were raised during the procedure relating to PMI, biowaiver for additional strengths, dissolution limit and risk assessment for potential nitrosamine impurities. The responses were all deemed satisfactory, and the MOs considered fulfilled.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

Aficamten (CK-3773274) is a small molecule allosteric cardiac myosin inhibitor designed to reduce the hypercontractility alleviating obstruction of the left ventricular outflow tract (LVOT) in patients with symptomatic hypertrophic cardiomyopathy (HCM).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In cell cultures in vitro, aficamten was demonstrated to inhibit the adenosine triphosphatase (ATPase) activity of bovine cardiac myofibrils with an IC50 of 1.26 µM. Aficamten inhibited the ATPase activity of purified myosin enzymatic domain with similar potency in absence of other sarcomere proteins, indicating a direct effect on cardiac myosin. Modest inhibition in fast skeletal muscle myosin from rabbit (basal IC50: 6.52) but not chicken smooth muscle was observed, indicating that aficamten is selective for the cardiac isoform of myosin compared to fast skeletal myosin. Aficamten inhibited bovine slow skeletal myofibril ATPase activity with similar potency as bovine cardiac muscle (IC50 1.23 µM), which was expected given the fact that cardiac and slow skeletal muscle express the same myosin isoform. In electrically paced, isolated rat ventricular cardiomyocytes, aficamten reduced the cellular contractility to 34.9% of the vehicle control, indicating that inhibition of cardiac myofibrillar ATPase activity translates into reduced LVFS. Calcium transients remained unchanged in cardiomyocytes treated with aficamten versus controls, confirming that decreases in contractility were due to effects downstream of the calcium transient at the level of the sarcomere. Furthermore, aficamten inhibited contractility of both wildtype and MYH7 R403Q(+/-) human engineered heart tissues. Potency of inhibition was in the same range as observed for bovine cardiac myofibril ATPase activity, although the potency against MYH7 R403Q(+/-) EHTs was modestly less.

A series of studies was performed to evaluate pharmacokinetic and pharmacodynamic effects of aficamten in healthy and diseased animal models in vivo. In healthy rats and dogs, aficamten decreased left ventricular contractility in a dose- and concentration-dependent manner as assessed by echocardiography.

In a single-dose study in rats, the LVFS at 1 hour was significantly reduced by all doses evaluated (0.5, 1, 2 and 4 mg/kg). LVFS reduction was dose- and plasma concentration dependent with an IC50 of 7.9 µM total plasma concentration (142 nM free plasma concentration) and an IC10 of 0.8 µM total plasma concentration (14.4 nM free plasma). The IC50 to IC10 ratio was approximately 10. The LVFS was fully recovered 24 h after a single oral dose at all dose levels. In a 10-day repeat-dose study in rats, in which animals received a 1, 3, and 6 mg/kg dose once daily, LVFS was significantly reduced 2 hours postdose at all three dose levels with greatest effect observed in the high dose group and lowest effect in the 1 mg/kg group. Of note, 2 hours post dosing there was no difference in LVFS between Day 4 and Day 10. Aficamten free plasma concentrations on Day 10 1 hr postdose in the 1, 3, and 6 mg/kg dose groups were 52 ± 12 nM, 159 ± 31 nM, and 370 ± 24 nM, respectively, and were in the same range on Day 4 versus. Ventricular contractility returned to baseline levels by 24 hours after the last dose on Day 10. Of note, in a separate study in healthy rats it was shown that IV administration of the β-agonist dobutamine was able to reverse the inhibition of cardiac contractility by 2 mg/kg aficamten within 5 to 30 minutes.

In healthy dogs, aficamten reduced cardiac contractility in a dose-dependent manner 2 hours following a single PO dose of 0.75, 2, or 3 mg/kg. The IC50 for LVEF was 1.3 µM or 324 nM free drug based on 24.9% unbound fraction value. Ventricular contractility also reversed over time but was a slower process due to the longer half-life of aficamten in dogs. At the last time point evaluated (48 h post-dose) no complete recovery was observed in the 2 and 3 mg/kg dose groups.

Aficamten was studied in the myosin heavy chain R403Q HCM mouse model that shows significant cardiac hypertrophy relative to wild type (WT) mice. Single oral doses of aficamten decreased LVFS from baseline and returned to baseline LVFS values 24 hours post-dose in this model. No difference in baseline or aficamten-mediated LVFS reduction was observed in WT versus R403Q animals. The IC50 for LVFS was 0.9 µM (140 nM free) for WT mice versus 0.78 µM (122 nM free) for R403Q mice. LVFS returned to pre-dose baseline values 24 hours post-dose at all dose levels in WT and R403Q mice.

Finally, the effect of aficamten was evaluated in HCM cats with an A31P mutation on cardiac myosin binding protein C. These animals showed cardiac hypercontractility and LVOT obstruction, similar to clinical symptoms of oHCM. A single dose of 0.3 or 1 mg/kg aficamten reduced both LVFS and LVOT gradient versus vehicle treated animals for up to 24 hours post-dose.

2.5.2.2. Secondary pharmacodynamic studies

Potential off-target effects of aficamten were evaluated in a ligand binding screen against 68 receptors, ion channels, and enzymes. At a concentration of 100 µM (33,700 ng/mL), binding of aficamten to a limited number of targets was observed, including the cannabinoid CB1, dopamine D4.2, and serotonin (5-Hydroxytryptamine) 5 HT2B receptors. In follow-up assays, aficamten showed no agonist activity in a 5-HT2B -dependent cell proliferation assay. In the presence of 30 nM serotonin, aficamten inhibited 5-HT2B-dependent cell proliferation with an IC50 of 81.8 µM (27,600 ng/mL). Furthermore, aficamten at a fixed concentration of 100 µM did not significantly increase GTPγS binding in cells overexpressing human cannabinoid CB1 receptor or human dopamine D4.2 receptors, while only marginal inhibition of CP 55,940- or dopamine-induced GTPγS binding was observed.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies in rats were conducted with oral doses of aficamten up to 9 mg/kg/day, which was the maximum tolerated dose in acute studies. Although the exposure in this study was not evaluated, the exposure in a single dose study in male rats, in which aficamten was given at a dose of 8 mg/kg was used for comparison. The mean Cmax value in this study was 8437 ng/mL. The free fraction of 135 ng/mL (based on an average plasma protein binding of 98.4% in rat) represents approximately 4-fold the predicted maximal clinical Cmax of the unbound fraction (34.1 ng/mL based on an average plasma protein binding of 89.6% in human).

No CNS or respiratory effects were noted at doses up to 3 mg/kg. At 9 mg/kg, CNS effects of aficamten were observed, including decreases in alertness and arena rearing counts, slightly drooping eyelids, and decreased body temperature at 1 and 4 hours postdose. In a respiratory study in rats, increased respiratory rate and decreased tidal volume were observed at a dose of 9 mg/kg. The observed CNS and respiratory effects in rats, except for drooping eyelids, were transient and resolved by 24 hours post dose.

Cardiovascular safety pharmacology of aficamten was evaluated in a series of in vitro and in vivo studies. The IC50 for the inhibitory effect of aficamten on hERG potassium current was not calculated due to the solubility limit of aficamten in assay vehicle but was estimated to be greater than 10 µM,

which is equivalent to a concentration of more than 180-fold the predicted maximal clinical Cmax (328 ng/mL total or 0.054 µM free) at the 20 mg QD dose in patients with oHCM.

In a study in conscious telemetered dogs, aficamten was administered orally for 7 consecutive days at doses up to 2 mg/kg/day. Cardiovascular parameters were evaluated for all animals beginning 2 hours prior to and continuing for up to 24 hours postdose on Days 1 and 7. Aficamten-related hemodynamic effects in telemetered dogs included transient decreases in the maximum rate of left ventricular contraction at all dose levels on Days 1 and 7, transiently increased heart rate (HR) and decreased systolic and pulse pressures at 1 mg/kg/day on Day 1 and 2 mg/kg/day on Days 1 and 7. There was also an increase in 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 changes were transient and resolved by 6 hours postdose. There were no aficamten-related effects on quantitative or qualitative ECG parameters at any dose level evaluated on either Day 1 or Day 7.

2.5.2.4. Pharmacodynamic drug interactions

Aficamten has not been evaluated in non-clinical pharmacodynamics drug interaction studies.

2.5.3. Pharmacokinetics

2.5.3.1. Method validation

LC-MS/MS methods were developed for the quantification of aficamten in plasma of mouse, rat, dog, and rabbit. Full method validations were presented for rat, rabbit and dog, whereas partial validation was performed for mouse and rat, which were based on the fully validated method for rabbit. The calibration ranges were 3.00 - 3000 ng/mL for mouse, rat and rabbit and 1.00 - 1000 ng/mL for dog. These LC-MS/MS methods were sensitive, selective, accurate, and reproducible, and long-term storage stability upon storage was also established. GLP was claimed for the mouse and rabbit method validations, as well as for two partly validated rat method validations (used in EFD and carcinogenicity studies). No GLP was claimed for the rat and dog method validations used in repeat-dose toxicity studies for both pivotal toxicity species (rat 28 days, 13 weeks and 26 weeks and dog 28 days, 13 weeks and 39 weeks), however these method validations were assessed to be in line with the relevant ICH guideline on bioanalytical method validation (ICH M10) and were therefore considered fit for purpose.

LC-MS/MS methods were also developed for the quantification of the main circulating diastereomer metabolites of aficamten: M1a and M1b. Full method validations were presented for rat plasma, whereas partial validation was performed for mouse and rabbit plasma (based on full validation for rat). For rat, the calibration ranges were 1.00-500 ng/mL for both analytes in the method used in the EFD, 6-week repeat-dose, 2-year carcinogenicity and PPND studies, and 8.00-2000 ng/mL (M1a) and 2.00-500 ng/mL (M1b) for the method used in the 13-week repeat-dose study. For mouse and rabbit plasma, the calibration ranges were 1.00-500 ng/mL. These LC-MS/MS methods were sensitive, selective, accurate, and reproducible, and long-term storage stability upon storage was also established. GLP was claimed for all method validations, except one of the rat method validations, which was assessed to be in line with the relevant ICH M10 guideline on bioanalytical method validation and was therefore considered fit for purpose.

2.5.3.2. Absorption

Single-dose studies

Intravenous studies in mouse, rat, dog and monkey revealed that mean plasma clearance (CL) was low, with values of 8.81, 2.09, 3.30, and 11.2 mL/min/kg, respectively. Mean steady-state volume of distribution (Vss) was high, with values reported at 3.14, 0.53, 10.5, and 7.76 L/kg in the mouse, rat, dog, and monkey, respectively. Together, this resulted in reported in long half-life values of 4.52, 2.99, 33.8, and 8.14 hours for mouse, rat, dog, and monkey, respectively.

Oral dosing in mouse, rat, rabbit, dog and monkey revealed that aficamten was rapidly absorbed, with t_{max} values reported between 0.25 and 1.17 hours for all four species tested. The absolute bioavailabilities were relatively high, with values reported at 41% in monkey, 45.2% in dog, 55-79% in rat and 97.5% in mouse. For rat and rabbit, increases in dose resulted in dose-proportional increases in C_{max} and AUC values.

Multiple dose studies (toxicokinetics studies)

In male and female transgenic rasH2 mice, toxicokinetics of aficamten, M1a and M1b were evaluated after daily administration of 0.5-2.0 mg/kg aficamten for 28 days and 26 weeks. In general, exposure of all three compounds increased in a dose proportional manner, with no apparent differences between males and females and no relevant accumulation after 26 weeks of dosing. In the 26-week study, exposure to M1a and M1b (combined sexes), based on AUC_{0-t}, ranged from 10.3% to 21.2% and 29.9% to 34.3%, respectively, compared to parent compound.

In pregnant rats, daily dosing of 2-9 mg/kg for 12 days (Day 6 to Day 17 postcoitum) revealed dose-proportional increases in C_{max} and AUC_{0-t} of aficamten, M1a and M1b, with no relevant accumulation observed after 12 days.

In juvenile rats, daily dosing of 1-6 mg/kg revealed dose-proportional increases in aficamten, M1a and M1b C_{max} and AUC_{0-t}, without relevant differences between males and females. No or low relevant accumulation was observed for aficamten (accumulation ratios ≤1.6), M1a (accumulation ratios ≤2.9) or M1b (accumulation ratios ≤1.5). The exposure to M1a, based on AUC_{0-24}, represented less than 6.0% of parent compound and exposure to M1b represented less than 25% of parent compound.

In the 1 year repeat-dose study in rats dosed with 0.5-2.0 (males) or 0.5-3.0 (females) mg/kg, dose proportional increases in aficamten, M1a and M1b C_{max} and AUC_{0-t} were observed, without relevant differences between males and females. No relevant accumulation was observed for aficamten (accumulation ratios ≤2.2), M1a (accumulation ratios ≤1.5) or M1b (accumulation ratios ≤1.6). The exposure to M1a, based on AUC_{0-t}, represented less than 5.0% of parent compound and exposure to M1b represented less than 17% of parent compound. Other repeat-dose studies in adult rats (28 days, 13 weeks, 26 weeks) showed similar results.

In pregnant rabbits receiving 5-15 mg/kg for 13 days (Day 7 to Day 19 pc), dose-proportional increases in aficamten, M1a, and M1b C_{max} and AUC_{0-t} were observed on Day 19. No relevant accumulation was observed for any of the compounds, with accumulation ratios ≤1.5 on Day 19. Exposure to M1a and M1b was very high compared to aficamten: based on AUC_{0-t}, M1a represented ~4800-13000% of parent compound and M1b represented ~3700-7600% of parent compound.

In the 39 weeks study in dogs dosed daily with 0.25-1 mg/kg, dose-proportional increases in C_{max} and AUC_{0-t} for aficamten were observed, without relevant differences between males and females, and no or only mild accumulation over time, with accumulation ratios at 39 weeks ≤3.0. Similar results were obtained for the 28 days and 13 weeks studies. M1a and M1b were not quantified in any of the dog studies.

2.5.3.3. Distribution

Plasma protein binding

Plasma protein binding of aficamten at 0.5, 2, and 10 µM (~0.17–3.4 µg/mL) was assessed in human, rat (Sprague Dawley), dog (beagle), monkey (cynomolgus), rabbit (New Zealand White), and mouse (C57BL/6) plasma using a rapid equilibrium dialysis method. Plasma protein binding was not concentration dependent for any of the species tested, with mean values reported at 89.6% (human), 98.4% (rat), 75.1% (dog), 83.8% (monkey), 89.6% (rabbit) and 84.5% (mouse). The corresponding free fractions were 15.5%, 1.6%, 10.4%, 24.9%, 16.2%, and 10.4% for mouse, rat, rabbit, dog, monkey, and human, respectively. These values indicate significant differences between the various species and human with regard to plasma protein binding, highlighting the need for corrected exposure multiples.

Regarding the metabolites M1a and M1b, plasma protein binding was assessed at 0.5, 2, and 10 µM (~0.18–3.5 µg/mL) in human, rat (Sprague Dawley), dog (beagle), rabbit (New Zealand White), and mouse (C57BL/6) plasma using a rapid equilibrium dialysis method. Plasma protein binding was not concentration dependent for both compounds for any of the species tested. M1a mean values were 82.7% (human), 85.9% (rat), 44.0% (dog), 78.0% (rabbit) and 64.3% (mouse tested at 10 µM only). M1b mean values were 93.0% (human), 89.3% (rat), 42.7% (dog), 80.0% (rabbit) and 66.2% (mouse tested at 10 µM only). These values indicate significant differences between the various species and human with regard to plasma protein binding, highlighting the need for corrected exposure multiples.

Whole blood to plasma partitioning

Aficamten whole blood to plasma ratios at 1 and 10 µM (~0.34 and 3.4 µg/mL) were 0.93 and 0.94 (human), 0.64 and 0.74 (rat), 1.18 and 1.10 (dog), 0.91 and 0.89 (monkey), 0.81 and 0.85 (mouse) and 0.87 and 0.90 (rabbit), respectively. Taking into account differences in haematocrit between species, aficamten distribution to red blood cells was calculated to be highest in mouse and dog at ~51% and ~44%, respectively, with human, monkey and rabbit at ~28-34%, and ~16-27% for rat. Aficamten was therefore shown to distribute to plasma predominantly.

M1a whole blood to plasma ratios at 1 and 10 µM (~0.35 and 3.5 µg/mL) were 0.77 and 0.79 (human), 0.81 and 0.80 (rat), 1.05 and 1.05 (dog), 1.02 and 1.00 (monkey), 0.98 and 0.97 (mouse) and 0.79 and 0.79 (rabbit), respectively. Taking into account differences in haematocrit between species, M1a distribution to red blood cells was calculated to be highest in mouse at ~58%, with rat, dog and monkey at ~33-41%, and ~17-20% for human and rabbit. M1a was therefore shown to distribute to plasma predominantly.

M1b whole blood to plasma ratios at 1 and 10 µM (~0.35 and 3.5 µg/mL) were 0.67 and 0.67 (human), 0.71 and 0.72 (rat), 0.99 and 1.03 (dog), 0.99 and 0.94 (monkey), 0.96 and 0.98 (mouse) and 0.78 and 0.76 (rabbit), respectively. Taking into account haematocrit differences between species, M1b distributing to red blood cells was calculated to be highest in mouse at ~58%, with dog and monkey at ~35-39%, rabbit and rat at ~17-25%, and ~5% for human. Therefore, M1b was shown distribute to plasma predominantly.

Tissue distribution in rats in selected organs

Distribution of aficamten to plasma, heart, gastrocnemius muscle, liver, brain and CSF was evaluated at 1, 4 and 6 hr following a single oral dose of 10 mg/kg aficamten to male Sprague Dawley rats. The tissue:plasma ratios based on AUC0-6hr for heart, liver, gastrocnemius muscle, brain and CSF were 1.42, 0.282, 0.700, 0.031 and 0.005, respectively. These results suggest the distribution of aficamten was highest in the heart and lowest in the CSF.

Quantitative Whole-body Autoradiography in Nonpigmented and Pigmented Rats

Distribution of a single dose of 8 mg/kg [^{14}C]-aficamten to male Sprague Dawley rats (nonpigmented) was studied using quantitative whole body autoradiography (QWBA) up to 168 hours post-dosing. Radioactivity was widely distributed, with the majority of the tissues reaching the maximum concentration after 1 to 4 hours. Radioactivity was preferentially distributed into muscular tissues, with the highest concentrations observed in muscle (semitendinous), myocardium, muscle, diaphragm, fascia, and liver. The highest tissue:plasma concentration ratios (t:p) were observed in nasal turbinates (t:p 6.9), arterial wall (t:p 5.2), cecum (t:p 4.0), myocardium (t:p 2.2), and muscle (semitendinosus) (t:p 1.8). Low levels of radioactivity were detected in brain (t:p 0.04) and testes (t:p 0.09), suggesting that [^{14}C]-aficamten-derived radioactivity crossed the blood:brain and blood:testis barriers. Radioactivity was cleared from all the tissues by 168 hours postdose, with the exception of arterial wall, intervertebral ligament(s), and nasal turbinates.

A single dose of 8 mg/kg [^{14}C]-aficamten given to Long Evans rats (pigmented) with QWBA up to 840 hours revealed a similar distribution of radioactivity to SD rats, with preferential distribution into muscular tissues. The highest concentrations were observed in myocardium, muscle (semitendinous), diaphragm, fascia, muscle, fat (abdominal), eye uveal tract, and liver. The highest tissue:plasma concentration ratios were observed in eye uveal tract (t:p 6.1), cecum (t:p 3.8), intervertebral ligament(s) (t:p 2.7), and large intestine (t:p 2.6). Radioactivity was cleared from all the tissues by 168 hours postdose, except for the arterial wall, eye uveal tract, eye(s), intervertebral ligaments, and nasal turbinates. By 840 hours, radioactivity was still quantifiable in arterial wall, eye uveal tract, and intervertebral ligaments. Pigmented skin showed higher concentrations of radioactivity than nonpigmented skin, which, together with the prolonged presence of radioactivity in eye uveal tract, indicated (reversible) melanin binding.

2.5.3.4. Metabolism

Metabolic stability in liver microsomes

Aficamten was incubated at 1 µM for up to 60 minutes with rat, dog monkey and human liver microsomes. The *in vitro* half-lives of aficamten were greater than 60 minutes for rat, dog and human liver microsomes but only 14.3 minutes for monkey liver microsomes. The calculated *in vitro* hepatic intrinsic clearance for rat, dog, monkey and human liver microsomes were <20.8, <16.6, 69.6, and <10.4 mL/min/kg, respectively.

In Vitro *Clearance of Aficamten in Hurelrat™ Rat, Hureldog™ Dog, and Hurelhuman™ Human Plated Hepatocytes*

Aficamten at 0.5 µM was incubated with the plated Hurelrat™ hepatocyte model, Hureldog™ hepatic coculture model, and Hurelhuman™ hepatocyte microliver model over a 72-hour time period at 37°C, and supernatants were processed and analyzed using LC-MS/MS. Half-live values of aficamten were 25.21 hours for rat, 78.77 hours for dog and 144.41 hours for human. Based on the calculated *in vitro* apparent intrinsic clearance ($CL_{int,app}$) values, the predicted *in vivo* plasma clearances $CL_{H,pred,plasma}$ for various species were 5.79 (rat), 2.94 (dog), and 0.69 (human) mL/min/kg. These values were in the range of the observed *in vivo* CL_{plasma} (see also 3.2 Absorption) of 2.09 and 3.30 mL/min/kg for rat and dog, respectively. Given the relatively accurate prediction of *in vivo* clearance in rat and dog based on *in vitro* data, this suggests that hepatic clearance of aficamten is the predominant clearance pathway *in vivo* for both nonclinical species.

Metabolite Profiling in Liver Microsomes and Hepatocytes

Following incubation of 20 µM aficamten with liver microsomes from rat, dog, monkey, and human for 60 minutes in the presence of NADPH, three metabolites were detected. M1 was a mono-hydroxylated derivative on the alpha carbon of the ethyl side chain linked to 1,2,4-oxadiazole. M2 was the dehydrogenated derivative in the dihydro-indenyl moiety. M3 was a mono-hydroxylated derivative at the dihydro-indenyl moiety. M1 was the most abundant, detected in liver microsomes prepared from all four species. M2 was detected at low levels in rat microsomes only. M3 was present at low levels in rat, monkey and human microsomes. These results showed that all metabolites detected in human liver microsomes were also detected in liver microsomes from the nonclinical species used in toxicity studies. Analysis of the relative amounts of the two diastereomeric metabolites of M1, specifically M1a and M1b, formed across rat, dog, monkey and human liver microsomes revealed stereoselective formation of M1a over M1b in rat and dog liver microsomes (4.2- and 1.5-fold, respectively) and stereoselective formation of M1b over M1a in monkey and human liver microsomes (2.7- and 2.0-fold, respectively).

Following incubation of 20 µM aficamten with hepatocytes from rat, dog, monkey, and human, six metabolites were detected. Metabolite M1 was found in hepatocytes of all species and was the most abundant metabolite. M2 was detected only in rat hepatocytes, and M3 was detected in rat, monkey and human hepatocytes. In addition, M4, a mono-hydroxylated derivative on the beta carbon of the ethyl side chain linked to 1,2,4-oxadiazole was identified in the dog hepatocyte incubate. Two glucuronides (M5 and M6) were identified at low levels. Both were tentatively identified as O-glucuronides of mono-hydroxylated metabolites on the ethyl side chain linked to 1,2,4-oxadiazole. M5 was found in rat and monkey hepatocytes, and at trace levels in human hepatocytes. M6 was detected in monkey hepatocytes only, and at trace levels in human hepatocytes. M7 was identified as a M1-sulfonate and was observed in trace amounts in all four species tested. These results revealed that all metabolites formed by human hepatocytes were also formed by hepatocytes from the nonclinical species.

Metabolite Profiling in Rat, Dog, and Monkey Plasma and rat urine

Metabolite profiling was performed on pooled plasma samples from rat (15-240 min after oral dose of 8 mg/kg), dog (30-240 minutes after oral dose of 4 mg/kg) and monkey (0.25-240 min after oral dose of 1 mg/kg) single dose studies. Additionally, a pooled urine sample (0-24 hours) from a rat excretion study was included. Consistent with the *in vitro* results from microsomes and hepatocytes, M1 was found in plasma of all three species and was the most abundant metabolite. M2 was detected only in rat plasma, M3 was present in rat, dog, and monkey plasma, and M4 was found only in dog plasma. The O-glucuronides M5 and M6 were found in rat plasma only. M1, M2, M3 and M5 found in rat plasma were also detected in the urine sample. In conclusion, all metabolites produced by human liver microsomes and hepatocytes were also found in the nonclinical species *in vivo*.

Metabolite Profiling in Plasma Collected in the 13-week Repeat PO Dose Rat Toxicology Study

Pooled plasma samples (AUC_{0-24}) from rats at Day 91 of rats receiving 3 (males) or 6 mg/kg (females) daily doses were analyzed using LC-MS/MS (positive mode ionization) for metabolite formation. In males and females, parent compound constituted 72 and 52 % of the total peak area, respectively. The unresolved mixture of M1a/M1b constituted 15% (males) and 30% (females) of the total peak area. Four other identified peaks (M2, M3 and two Hydroxy-aficamten-glucuronides) each accounted for <5% of total peak area for males, and for <11% of total peak area for females.

Metabolite Profiling in Plasma, Urine, and Feces of Intact Rats and in Urine, Feces, and Bile of BDC Rats After Single PO Administration of [^{14}C]-aficamten

In male rats, LC-MS analysis of $AUC_{(0\text{-}24\text{-}48)}$ hours pooled plasma samples after a single dose of 8 mg/kg [^{14}C]-aficamten revealed six radioactive peaks (each >1% of the total radioactivity exposure) that were identified as aficamten and its metabolites by comparison with reference standards.
Unchanged aficamten was the major circulating component and accounted for approximately 80% of the sample radioactivity in pooled plasma. The M1a/M1b mixture was the second major circulating component and accounted for approximately 12% of sample radioactivity. Other minor metabolites identified were M2, M3, M5, and M45, each contributing <4% of sample radioactivity.
Renal elimination was a minor route of excretion after oral dosing. Trace levels of unchanged aficamten were detected in urine. M5, M3, and the M1a/M1b mixture were the abundant metabolites in urine, although all three were <1.5% of radioactive dose.
Hepatobiliary excretion was the major route of elimination of radioactivity after oral dosing. Trace levels of unchanged aficamten were recovered in bile. M5 was the major component in bile and accounted for 35.2% of the radioactive dose, with M7 and M6 responsible for 9.6% and 2.6% of the radioactive dose, respectively.
In feces of intact rats, the most abundant components were M18 (~35% of administered dose), M45 (7.2% of administered dose) and M9 (~5.4% of administered dose). In feces of BDC rats, the most abundant components were M18 (~7.1% of administered dose), M45 (3.7% of administered dose) and M9 (~2.8% of administered dose). No unchanged aficamten was observed in feces of intact or BDC rats.

Characterization of the Metabolic Route of Formation for Metabolite M18 in Feces in BDC Rats

Male bile duct-cannulated rats receiving a single oral dose of 8 mg/kg aficamten were used to collect bile over a 24-hour period. These bile samples (containing the glucuronide conjugate M5) were added to a mixture of rat intestinal contents and incubated over a 20-hour period under anaerobic conditions at 37°C. This resulted in complete degradation of M5 and corresponding formation of M18. Therefore, metabolite M18 detected in rat feces from aficamten-dosed rats is hypothesized to be formed via a pathway that starts with formation of the hydroxylated aficamten metabolite M1a, followed by glucuronidation leading to the glucuronide-linked metabolite M5 in liver, subsequent biliary excretion of M5 into intestine with successive metabolism by intestinal microbiota leading to metabolite M18 (corresponding to ~35% of administered dose).

Proposed metabolic pathway

The proposed metabolic pathway, based on studies in microsomes, hepatocytes and an *in vivo* mass balance study in rats, includes CYP450-mediated hydroxylation of aficamten, resulting in formation of four different hydroxylated metabolites: diastereomers M1a and M1b, M3 and M4. M3 is subsequently converted into M2 via a dehydration reaction. M1a and M1b (main metabolites present in plasma) are subsequently sulfonated to form M7/M64 or glucuronidated to form M5/M6 (main metabolites in bile). Metabolite M5 present in bile is then excreted into intestine and subsequently undergoes reduction and amide hydrolysis to form M18 (main metabolite in feces) and deglucuronidation to form M45.

CYP induction and inhibition

These studies are assessed in section pharmacokinetic interaction studies, refer to Clinical pharmacology.

2.5.3.5. Excretion

Excretion of Aficamten and its Metabolites M1a/M1b in Male Sprague Dawley Rats After Single Oral Administration

Following an oral dose of 10 mg/kg of aficamten in male Sprague Dawley rats, recoveries of aficamten in urine and feces in 24 hours were 0.034% and 0.015%, respectively. In addition, 1.35% and 0.001% dose equivalent of M1 was recovered. Following hydrolysis with β-glucuronidase, the recovery of M1 in urine and feces increased to 3.37% and 0.008% respectively. The total recovery of aficamten, M1 and glucuronide of M1 (probably M5) combined in urine and feces was approximately 5% following an oral dose of aficamten.

Excretion Mass Balance in Intact and Bile Duct-Cannulated Male Sprague Dawley Rats After Single Oral Administration of [^{14}C]-aficamten

Total radioactivity was quantified in excreta and cage rinse/wipe up to 168 hours after single oral administration of 8 mg/kg [^{14}C]-aficamten to fasted intact or bile duct-cannulated rats. In intact rats, the majority of radioactivity (>90% of dose) was excreted by 48 hours post dosing. After 168 hours, all radioactivity (>99%) was recovered. After 168 hours, approximately 91% of radioactive dose was recovered in feces and 8% in urine. In bile duct-cannulated rats, the majority of radioactivity (>90% of dose) was excreted by 48 hours post dosing. After 168 hours, recovery was complete (>98%), with ~52% of radioactivity recovered in bile, ~37% in feces and ~8% in urine. Together, these results indicate that excretion occurs primarily via metabolites in bile and subsequently feces, with only a minor role for renal excretion.

2.5.3.6. Pharmacokinetic drug interactions

See section 2.6 on Clinical aspects.

2.5.3.7. Other pharmacokinetic studies

No studies have been provided, this is agreed.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

In accordance with the ICH M3(R2) guideline, no dedicated single-dose toxicity studies were conducted with aficamten.

2.5.4.2. Repeat dose toxicity

Non-GLP compliant range finding studies in rats revealed no dose limiting toxicity when dosed up to 3 mg/kg/day for 10 days in presence of aficamten mediated exaggerated pharmacology. Similarly, non-GLP compliant range finding studies in dogs revealed no dose limiting toxicity when dosed up to 4 mg/kg/day for 10 days.

GLP compliant repeat dose toxicity rodent studies were conducted in Sprague Dawley rats. Studies were designed to evaluate aficamten mediated toxicity after 28 days, 13-weeks or 26-weeks following

oral dosing. GLP compliant repeat dose toxicity non-rodent studies were conducted in Beagle dogs. Studies were designed to evaluate aficamten mediated toxicity after 28 days, 13-weeks or 39-weeks following oral dosing. All studies included TK and recovery animals.

Administration of aficamten to rats and dogs up to 13 weeks results mainly in exaggerated pharmacological effects and was otherwise generally well tolerated. Heart is the main target organ of toxicity as noted by increased heart weight, dilatation of ventricles and myocardial degeneration. This was accompanied by a non-adverse increase in heart rate. In rats, atrial thrombosis was also observed in high dose males in the 13-week study, whereas in dogs papillary muscle fibrosis was noted in high dose animals in the 13-week study. Lung and liver were also target organs of toxicity in the rat. In lung, incidental lung haemorrhage was observed in a deceased male rat receiving 3 mg/kg aficamten per day in the 13-week RDT study. In surviving animals in this high dose group, increased lung weights were noted which correlated microscopically with diffuse alveolar pigmented macrophages. These findings were recoverable. Non-adverse weight loss was generally observed in dog as well. Exposures in the 28-day and 13-week RDT studies in rats and dogs were generally low. In the 13-week rat study, the NOAEL was considered to be 3.0 mg/kg/day for males and 6.0 mg/kg/day for females. At the NOAEL, and when corrected for plasma protein binding, exposure margins were approximately 2.5x 1.5-2x higher than the MRHD based on Cmax and AUC, respectively. In the 13-week dog study, the NOAEL for aficamten was considered to be 1.0 mg/kg/day. At the NOAEL, exposure margins were approximately 3x and 1.5x higher than the MRHD based on Cmax and AUC.

Surprisingly, the 26-week and 39-week RDT studies in rats and dogs, respectively, were virtually devoid of adverse effects. Anticipated aficamten related exaggerated pharmacology was also not observed. In absence of toxicologically meaningful findings, the NOAEL was the highest dose tested in both studies. For rat, the exposure margin at the NOAEL of 1.5 mg/kg/day is below 1 based on AUC. In dog, the exposure margin at the NOAEL of 1 mg/kg/day is approximately 1.5 based on AUC.

2.5.4.3. Genotoxicity

In a bacterial reverse mutation assay, aficamten was demonstrated to be not mutagenic. In an in vivo genotoxicity study conducted in rats, aficamten was negative for the induction of micronuclei in bone marrow polychromatic erythrocytes and, negative for the induction of DNA strand breakage in liver, as measured by an alkaline comet assay. Based on the results of the in vitro and in vivo tests, aficamten is concluded to be not genotoxic.

2.5.4.4. Carcinogenicity

The carcinogenic potential of aficamten was evaluated in a 26-week transgenic rasH2 mouse study and a 104-week rat carcinogenicity study. A GLP compliant 28-day repeat dose toxicity study was also conducted and supported the dosing strategy for the 26-week study.

In the 26-week transgenic rasH2 mouse study, there were no differences in incidence, onset or distribution of clinically observed palpable masses in aficamten-treated animals compared with the vehicle control group, nor were there aficamten-related macroscopic findings. As anticipated, heart weights in aficamten treated animals were increased. Microscopic examinations revealed no aficamten-related neoplastic or non-neoplastic findings in either sex at any dose level evaluated. Overall, this study suggested a low risk for carcinogenic potential of aficamten.

There were no apparent aficamten-related effects on clinical observation, body weight, body weight gain, food consumption, haematology or serum chemistry. Survival decreased in the high dose group due to aficamten mediated pharmacological effects on the heart. Survival was statistically significantly

different compared to controls. Dose administration of all surviving males and females at these dose levels was suspended as of Week 68 and Week 91, respectively Because of the low number of surviving animals, these were subsequently euthanised early (weeks 79-80 for males, week 96 for females). In controls and in lower dose groups, mortality was driven primarily by chronic progressive nephropathy mortality in male rats, and mammary fibroadenomas and pituitary adenomas in female rats. Control and lower dose groups (0.5 and 1 mg/kg/day) were euthanised early due to low survival. Scheduled euthanasia was conducted on in Weeks 100 and 101 for males, and in week 103 for females.

Non-neoplastic lesions were in line with anticipated effects of aficamten mediated inhibition of cardiac myosin. These observations were dose dependent and were particularly pronounced at higher doses. In addition to previous observations, fluid was observed in the chest cavity of dead or moribund euthanised animals, particularly in high dose animals. The fluid was most likely pleural effusion secondary to heart fibrosis and myocardial hypertrophy and lung fibrosis. Similar to the repeat dose toxicity studies, there was no evidence of the histopathological risk factors for neoplasia, namely cellular hypertrophy, cellular hyperplasia, tissue injury and/or inflammation, atypical cellular foci, or cellular changes with preneoplastic potential, up to maximum tolerated doses.

Examination of palpable masses showed a lack of an increase in aficamten treated animals compared to controls. Masses occurred more often in females than in males. Data were compared to site historical control data and tumour type and incidence was also compared to published data. According to the Applicant, there were no dose-related trends in the incidence of neoplastic findings in either sex at any aficamten dose level evaluated when compared to concurrent control animals or historical test facility reference data. Following 365 consecutive days of dosing with aficamten, exposure at AUClast was and 64900 h.ng/mL for males dosed at 2 mg/kg/day and 111000 h.ng/mL for females dosed at 3 mg/kg/day, respectively. This corresponds to an exposure margin of 1.3 and 2.2 at the MRHD in males and females, respectively.

2.5.4.5. Reproductive and developmental toxicity

The potential for aficamten-related effects on fertility were evaluated in rats. no aficamten-related mortality or clinical signs, nor were there effects on body weights, body weight gain, organ weights, mating, fertility, estrous cycling, ovarian or uterine findings, male reproductive assessments (organ weights), or embryo fetal survival at any dose level. Food consumption was transiently decreased in high dose males, but was not considered adverse. The absence of apparent exaggerated toxicology or adverse effects mediated by aficamten is a concern, since at the likely low exposure multiples, the study could be considered insufficient. The NOAEL for parental toxicity and fertility was 3.0 mg/kg/day in males and 6.0 mg/kg/day in females, while the no-observed-effect level (NOEL) for embryo-fetal development (EFD) was 6.0 mg/kg/day.

Embryofetal development was evaluated in rats and rabbits. In rats, pregnant dams were administered aficamten from GD6 through GD 17 with doses up to 9 mg/kg/day. All animals survived to the end of the study. There were no remarkable clinical or necropsy observations in dams. Heart weights were slightly increased in dams administered 6 mg/kg/day onwards, in line with previous observations and anticipated PD effects of aficamten. Dose dependent decreases in food consumption and corresponding decreased body weight gain and decreased body weight was noted. Body weight loss was considered adverse at 9 mg/kg/day. At 9 mg/kg/day, embryofetal toxicity was also noted and manifested as increased number of resorptions and early resorptions, increased post-implantation loss and decreased number of fetuses, as well as fewer live fetuses. These observations were outside of the historical control range of the test facility. Fetal examination showed decreased mean fetal weights in animals exposed to 9 mg/kg aficamten per day but were within historical control values of the test facility.

There were no aficamten-related external, visceral, or skeletal malformations or variations noted at any dose level evaluated. NOAELs for maternal toxicity and EFD were both considered to be 6 mg/kg/day, corresponding to a plasma protein binding corrected exposure margin of 5.6x and 2.5x based on Cmax and AUC, respectively. At the LOAEL in the rat EFD study, exposure margins are 4.9x and 1.9x above the MRHD based on Cmax and AUC, respectively and are therefore of clinical concern.

In rabbits, pregnant dams were administered aficamten from GD7 through GD 19 with doses up to 20 mg/kg/day. Due 4 early deaths, the high dose was reduced to 15 mg/kg aficamten per day between days 7 and 9. These deaths were considered to be aficamten-related. In surviving animals, there were no changes in clinical, pathological or reproductive parameters. There were no aficamten-related macroscopic findings or effects on heart weight at any dose level at the Day 29 scheduled necropsy. There were no aficamten-related effects on the number of corpora lutea, implantation sites, live fetuses, resorptions, sex ratio, and pre- and post-implantation losses (%) at any aficamten dose level. Mean fetal weight values (males, females, and sexes combined) were unaffected by aficamten administration, and there were no aficamten-related external, visceral, or skeletal malformations or variations noted at any dose level evaluated. The NOAEL for maternal toxicity was considered to be 10.0 mg/kg/day, and the NOAEL for EFD was considered to be 15.0 mg/kg/day. At the NOAEL, exposure margins for aficamten were approximately 1.2x and 0.1x higher than the MRHD based on Cmax and AUC.

Pre- and post-natal development effects of aficamten were evaluated in rats. Pregnant animals received up to 6 mg/kg aficamten per day. Animals were followed for two subsequent generations. All F0 generation females survived until scheduled termination with no aficamten-related maternal clinical observations during the gestation and/or lactation periods. Aficamten-related decreased body weight was observed in animals receiving 6 mg/kg/day. Heart weight was statistically increased in the high dose groups, but there was a trend towards increased heart weight in all dose groups. At the high dose, viability of pups was decreased. Surviving pups at this dose had an increased incidence of thin appearance, suspected dehydration, no milk band present, and bent tail were observed. Acoustic startle reflexes were also statistically significantly increased in the high dose group. There were no other toxicologically relevant aficamten-related effects on the general development of F1 generation males or females. The maternal NOAEL for aficamten was considered to be 1.5 mg/kg/day due to reductions in maternal body weight, increases in maternal heart weight, and a decreased pup viability index noted at 6.0 mg/kg/day. The NOAEL for aficamten on development, growth, and reproduction of F1 pups was also considered to be 1.5 mg/kg/day, based on adverse clinical observations, reduced preweaning body weight, and a slight delay in acoustic startle reflex during the preweaning period.

2.5.4.6. Toxicokinetic data

Toxicokinetics of aficamten was studied in the 28 days and 26 weeks repeat-dose studies in mice, in

28 days, 13 weeks, 26 weeks and 52 weeks repeat-dose as well as embryofetal and juvenile toxicity studies in rats, in the embryofetal study in rabbits, and in the 28 days, 13 weeks and 39 weeks

repeat-dose studies in dogs. Additionally, toxicokinetics of M1a and M1b were studied in the 28 days and 26 weeks repeat-dose studies in mice, in the 13 weeks and 52 weeks repeat-dose as well as embryofetal and juvenile toxicity studies in rats, and in the embryofetal study in rabbits.

In mice, exposure of aficamten, M1a and M1b increased in a dose-proportional manner, with no apparent differences between males and females and no relevant accumulation after 26 weeks of dosing. In the 26-weeks study, exposure to M1a and M1b ranged from 10.3-21.2% and 29.9-34.3% of parent compound, respectively.

In rats, exposure of aficamten, M1a and M1b increased dose-proportionally for all of the studies, with no relevant differences between males and females. Relevant accumulation was not observed for most of the studies, with accumulation ratios ≤1.5-2.9 for aficamten, M1a and M1b. Exposure to M1a ranged from 1.1-8.8% of parent compound and for M1b ranged from 10-30% of parent compound.

In the rabbit embryofetal study, dose-proportional increases in aficamten, M1a, and M1b Cmax and AUC0-t were observed. No relevant accumulation was observed for any of the compounds, with accumulation ratios ≤1.5. Exposure to M1a represented ~4800-13000% of parent compound and exposure to M1b represented ~3700-7600% compared of parent compound, indicating high exposure for metabolites.

In dogs, dose-proportional increases in aficamten Cmax and AUC0-t were observed, without relevant differences between males and females, and no or only mild accumulation over time, with accumulation ratios ≤2.5-3.0. M1a and M1b were not quantified in the dog toxicity studies.

2.5.4.7. Interspecies comparison and exposure multiples

Interspecies comparison

Absorption studies in mice, rats, dogs and monkeys revealed low clearance across species, with clearance values of 8.81, 2.09, 3.30, and 11.2 mL/min/kg, respectively. Volume of distribution (Vss) was high across species, with values reported at 3.14, 0.53, 10.5, and 7.76 L/kg in the mouse, rat, dog, and monkey, respectively. For humans, 4.4 L/kg was calculated based on a total volume of 309 L. Long half-life values of 4.52, 2.99, 33.8, and 8.14 hours were observed for mouse, rat, dog, and monkey, respectively, which is well below the half-life in humans of ~80 hours. Aficamten was rapidly absorbed, with t_{max} values reported between 0.25 and 1.17 hours for all four nonclinical species. The absolute bioavailabilities were relatively high: 41% in monkeys, 45.2% in dogs, 55-79% in rats and 97.5% in mice. Absolute bioavailability for humans was not reported. Across nonclinical species, no differences between males and females and no relevant accumulation was observed upon multiple dosing.

Plasma protein binding of aficamten not concentration dependent for any of the species tested, with mean values reported at 89.6% (human), 98.4% (rat), 75.1% (dog), 83.8% (monkey), 89.6% (rabbit) and 84.5% (mouse). Based on these differences, exposure multiples should be corrected for plasma protein binding, which results in markedly decreased exposure multiples for rat studies. Plasma protein binding of M1a showed mean values of 82.7% (human), 85.9% (rat), 44.0% (dog), 78.0% (rabbit) and 64.3% (mouse tested at 10 µM only). M1b plasma protein was reported at 93.0% (human), 89.3% (rat), 42.7% (dog), 80.0% (rabbit) and 66.2% (mouse tested at 10 µM only). Here also, exposure multiples should be corrected for plasma protein binding.

Taking into account differences in haematocrit between species, aficamten distribution to red blood cells was calculated to be highest in mouse and dog at ~51% and ~44%, respectively, with human, monkey and rabbit at ~28-34%, and ~16-27% for rat. M1a distribution to red blood cells was calculated to be highest in mouse at ~58%, with rat, dog and monkey at ~33-41%, and ~17-20% for human and rabbit. For M1b, distribution to red blood cells was calculated to be highest in mouse at ~58%, with dog and monkey at ~35-39%, rabbit and rat at ~17-25%, and ~5% for human. All three compounds distribute to plasma predominantly across species.

In the human [^{14}C]-aficamten mass balance study, several plasma metabolites were identified. M1a and M1b were the most abundant metabolites and accounted for a combined 46.9% of total radioactive exposure in the pooled human plasma sample. Chiral analysis of M1a/M1b identified M1a and M1b as contributing approximately 22% and 77% of the M1a/M1b radioactivity, respectively. M1 was also

detected in rat plasma (~12% of sample radioactivity), urine, feces, and bile, as well as in human urine. M3 was detected in human plasma at 0.23% of the pooled human plasma sample, and was also detected in rat plasma (~3.6%), urine, feces, and bile and in human urine. M5 was detected in human plasma at ~10.3% of the pooled plasma sample, and was also detected in rat plasma (~1%), urine, and bile (major) and in human urine. M64 (sulfonated M1) was detected in human plasma at ~1.3%, and not in rat plasma. In summary, all major human metabolites observed in plasma were also observed in rat plasma, except for M64. The major metabolites (>10% of total radioactivity) observed in human plasma were M1a, M1b, and M5. Of these, M5 is considered not to be of toxicological concern as it is a glucuronide conjugate. M1a and M1b are considered to be adequately characterized in nonclinical studies, given their exposure in rat toxicity studies, with AUC values >50% of human AUC, in line with the Q&A on ICH M3 (R2). Moreover, both are pharmacologically inactive when compared to parent compound.

Excretion in both humans and rats was mainly via metabolites that were excreted in the feces (~58% of radioactivity in humans, and ~90% of radioactivity in rats), with a minor role for urinary excretion (~30% of radioactivity in humans, and ~8% in rats). In bile duct-cannulated rats, ~52% of radioactivity was recovered in bile, ~37% in feces and ~8% in urine. Together, these results indicate that excretion in both species occurs primarily via bile and subsequently feces, with a minor role for renal excretion.

Exposure multiples

Exposure multiples were calculated and corrected for differences in protein plasma binding for the various species. In general, exposure multiples for aficamten were (very) low for all nonclinical species used in the toxicity studies, ranging from 0.03 (rabbit EFD) – 2.3 (rat 52 weeks), indicating that all findings in these studies must be considered clinically relevant.

For the two main metabolites, exposure multiples for all studies ranged from 0.27-5.6 for M1a and from 0.84-6.1 for M1b, indicating similar or higher exposure multiples when compared to aficamten. These exposure multiples are considered relevant for off-target effects only, as both metabolites are pharmacologically inactive.

2.5.4.8. Local Tolerance

No stand-alone local tolerance studies with aficamten have been conducted. As aficamten intended for oral administration to humans, the local tolerance of aficamten was thoroughly investigated in formal repeat dose mammalian toxicity studies via routine histopathologic evaluation of gastrointestinal tract tissues. The absence of local tolerance studies has been adequately justified.

2.5.4.9. Other toxicity studies

Aficamten is not phototoxic. Metabolites M1a and M1b have been adequately characterised in vivo. Neither is pharmacologically active at therapeutic exposure levels. In addition, metabolite M1a was non-mutagenic in a GLP-compliant bacterial reverse mutation assay. Metabolite M1a was considered clastogenic/aneugenic in a GLP-compliant micronucleus assay but did not induce DNA damage in vivo. Metabolite M1b was non-mutagenic nor clastogenic/aneugenic. For impurities controlled below the ICH qualification limit, refer to the quality assessment. A 13-week GLP compliant RDT in rats was conducted to qualify process impurity CK-4030838. At the highest dose tested, changes in pituitary gland, ovary, vagina and/or mammary gland were observed that could indicate alterations in the endocrine function of the hypothalamic-pituitary-gonadal axis. A qualification limit of 0.25% (0.00625

mg/kg/day) was set for CK-4030838, based on the effects observed in the female reproductive organs and the pituitary gland at a dose of 0.0125 mg/kg/day.

2.5.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): aficamten			
CAS-number (if available): 2364554-48-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.8	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw, default}$	0.1	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = sandy loam Soil 2 = sandy loam Soil 3 = clay Sludge 1 = Tilburg Sludge 2 = Aa & Maas	OECD 106	$K_{FOC, soil\ 1}$ = 483 L/kg_{oc} $K_{FOC, soil\ 2}$ = 644 L/kg_{oc} $K_{FOC, soil\ 3}$ = 635 L/kg_{oc} $K_{FOC, sludge\ 1}$ = 157 L/kg_{oc} $K_{FOC, sludge\ 2}$ = 142 L/kg_{oc}	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = loam Sediment 2 = sand	OECD 308	$DT_{50, water}$ = 6.1 / 5.0 d $DT_{50, sediment}$ = X / X d $DT_{50, whole\ system}$ = 7.04 / 17.7 d shifting to sediment = 23 / 33.5% CO_2 = 0.2 / 0.2 % NER = 71.1 / 81.9%	DT50s at 12°C 1 / 2 at day 4 / 3 at test end at test end

		Transformation products >10% = Y TP = 35.9 / 19.3 %, DT50 TP: ≥165 / ≥121 d			
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	EC_{10}	540	µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	EC_{10}	480	µg/L	mortality
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	EC_{10}	83	µg/L	embryo survival
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	EC_{10}	3081	mg/kg_{dw}	normalized to 10% organic carbon

2.5.6. Discussion on non-clinical aspects

The proposed mode of action of aficamten was confirmed in vitro and in vivo using systems derived from a variety of species. The applicant considered the potency of inhibition of bovine cardiac myofibril ATPase activity by aficamten similar to that of human. Even though myosin orthologs from various species share relatively high amino acid identity (>90%) with human myosin, no binding data are presented for other species used during nonclinical development. Nevertheless, the high-resolution structure of aficamten complexed with the bovine cardiac myosin head domain allowed to identify critical cardiac myosin residues involved in aficamten binding. Subsequent sequence alignment of α and β cardiac myosin orthologs of human, bovine, dog, cat, rat, and mouse origin showed 100% conservation of critical binding residues. This justifies the selected species used in the nonclinical development program to be pharmacological and toxicological relevant. However, it cannot be excluded that differences in skeletal and cardiac myosin sequences outside the aficamten binding pocket could result in differential modulation of myosin activity in different species. The potency of aficamten to inhibit the contractility of MYH7 R403Q(+/) EHTs was modestly less than observed for wildtype EHTs. However, the impact of other common pathogenic mutations in the β-cardiac myosin gene MYH7 involved in HCM, including R453C, R719W, R723G, and G741E, on the functional activity of aficamten is currently unclear. Nevertheless, structural analysis revealed that the mutations R453C, R719W, R723G, and G741E do not directly interfere with aficamten binding and are unlikely to significantly affect aficamten potency.

A series of studies was performed to evaluate pharmacokinetic and pharmacodynamic effects of aficamten in healthy and diseased animal models in vivo. In healthy rats and dogs, aficamten decreased left ventricular contractility in a dose- and concentration-dependent manner as assessed by echocardiography. Ventricular contractility returned to baseline levels by 24 hours after the last dose in single-dose and repeat-dose studies in rat, demonstrating reversibility of the PD response 24 h after the last dose in a repeat-dose study in in healthy rats. Inhibited ventricular contractility in dogs also reversed over time but was a slower process due to the longer half-life of aficamten in dogs. Of note, at the last time point evaluated (48 h post-dose), no complete recovery was observed in the 2 and 3 mg/kg dose groups.

Aficamten also showed functional activity in disease models of HCM in vivo. In the myosin heavy chain R403Q HCM mouse model, single oral doses of aficamten induced a dose-dependent, reversible decrease of LVFS from baseline. R403Q HCM mice show significant cardiac hypertrophy, but no functional differences of aficamten on cardiac contractility were noted compared with WT mice. Furthermore, the reduction of LVFS and LVOT gradient in HCM cats with an A31P mutation indicated that the reduction in contractility and corresponding decrease in the LVOT gradient by aficamten resulted in decreased outflow tract obstruction. Together these data provide proof of concept for the potential of aficamten to alleviate symptoms of oHCM.

Off-target effects of aficamten in the ligand binding screen were observed only at concentrations (81.8 – 100 µM [27,600 - 33,700 ng/mL]) that were much higher than the predicted maximal clinical C_{max} (328 ng/mL total; 0.054 µM free) and indicate specificity for cardiac myosin.

Secondary targets were selected based on the Eurofins LeadProfilingScreen panel, which aligns with ICH S7A guidance and industry standards for off-target pharmacology screening. The panel covers a broad range of receptors, ion channels, and enzymes relevant to CNS and cardiovascular safety. Testing was performed at a supratherapeutic concentration (100 µM), providing a large safety margin, and no significant binding was observed for any ion channel, except for the mandatory hERG evaluation per ICH S7B. Further supportive functional data in primary rat cardiomyocytes confirmed no off-target effects on calcium handling. The potential of aficamten inducing off-target effects on other tissues outside the heart is considered low. Reduced alertness that was observed in rats treated with 9 mg/kg aficamten is considered to be an indirect, secondary effect resulting from excessive reduction in cardiac contractility at this supra-pharmacological dose (safety margin=~7), rather than a direct CNS effect.

In addition to CNS effects, safety pharmacology studies showed respiratory effects, such as increased respiratory rate and decreased tidal volume, which may be compensatory mechanisms for the effect of aficamten on the heart. Aficamten-mediated hemodynamic and cardiovascular changes were consistent with its primary mechanism of action to reduce cardiac contractility resulting in reduced LVFS, ejection fraction, and stroke volume. Increased heart rate, which resulted in increased left ventricular end diastolic pressure and decreased -dP/dt, were expected and transient compensatory mechanisms.

Method validation reports were provided for all species.
In multiple dose studies performed in mice, rats, and dogs, there were no meaningful differences between males and females, and accumulation upon multiple dosing was generally absent or low, with accumulation ratios ≤2.0-3.0. There were marked differences in protein plasma binding between species, which should be taken into account for calculation of exposure multiples. Tissue distribution was wide and fast, with radioactivity associated with [^{14}C]-aficamten dosing distributing mainly to muscle (semitendinous), myocardium, muscle, diaphragm, fascia, and liver, indicating delivery to the target organs.
Metabolism of aficamten was extensive across species, with three major metabolites (>10% of total radioactivity) identified in humans: M1a, M1b and M5. All three were also identified in rat plasma. Of

these, M5 is considered not to be of toxicological concern as it is a glucuronide conjugate. M1a and M1b are considered to be adequately characterized in nonclinical studies, given their exposure in rat toxicity studies, with AUC values >50% of human AUC, in line with the Q&A on ICH M3 (R2). Moreover, both are pharmacologically inactive when compared to parent compound.
Excretion of aficamten in rats was mainly driven by metabolism and subsequent excretion via bile and feces, similar to humans. Renal excretion played only a minor role in rats, with ~8% of aficamten-associated radioactivity excreted in urine.

In both species, chronic RDT studies generally may not have explored the full range of aficamten mediated effects in naïve animals due to lack of exposure due to dose limiting aficamten-related (exaggerated) pharmacology. As a result, exposure margins in the chronic RDT studies in rat and dog are below what is expected in ICH M3(R2). High doses of aficamten for prolonged periods of time in naïve animals result in exaggerated and adverse pharmacology, as witnessed in the 104-week carcinogenicity study. As a result, dose selection for the 26-week rat and 39-week dog studies was based on minimal tolerable doses in the respective 13-week studies.

The high mortality in the 104-week carcinogenicity necessitated early termination of dose groups. However, under the conditions of this study, the number of surviving animals in the control, low and mid dose group allowed for an assessment of tumor incidence and that the utmost was done to provide a meaningful evaluation of tumor incidence in the high dose group. Furthermore, study data was compared to published historical control data, including a dataset that has corrected the incidence of neoplastic lesions for mortality (poly-3 adjusted incidence). The sometimes (very) high incidences of neoplasms in the concurrent controls as well as the incidence rates in the test facility remain rather surprising but overall, and taking into account datasets from Kumar and Morse, suggest this was likely an unfortunate case of variability skewing towards a higher incidence in the study and the test site. In the case of mammary gland fibroadenoma, the raw incidence exceeded raw incidence historical control literature data, test site facility historical control data and poly-3 adjusted incidence in absence of a dose response. However, while the high dose incidence was lower than the low- or mid dose incidence, it was slightly higher than the historical maximum in the poly-3 corrected dataset. In this case, the Applicant justified this increase to variability due to the fact there was no clear dose response, and the fact that high dose incidence was below concurrent and test-site control data. In the repeat dose toxicity studies, no early signs of carcinogenic risk such as hyperplasia were recorded. However, it was not feasible to achieve high exposures. The transgenic mouse data did not suggest carcinogenic risk and the available data does not suggest involvement of aficamten in pro-oncogenic pathways. Overall, the totality of evidence is sufficient to suggest that aficamten has a low carcinogenic potential.

Reproductive and developmental toxicity studies were also affected by dose limiting exposure as a result of exaggerated pharmacology in treated dams. As a consequence, exposure margins in these studies are consistently low.

Fertility and reproductive performance were not affected by aficamten in male and female rats.

When aficamten was administered orally in an embryo-foetal toxicity study in the rat, increases in the number of early and late resorptions, decreases in group mean foetal body weight, and foetal abnormalities such as short tail (1 foetus) and kinked tail (2 foetuses) were observed at maternally toxic exposures 2.5x above the maximum recommended human dose (MRHD) of 20 mg of aficamten based on AUC. There were no aficamten-associated adverse effects on foetal growth, or foetal external or visceral variations observed at exposures 1.9x above the MRHD based on AUC.

When aficamten was administered orally in an embryo-foetal toxicity study in the rabbit, increases in the number of late resorptions were observed at maternally toxic exposures below the MRHD. As such this study is considered insufficient.

In a pre- and postnatal development study, aficamten was administered to maternal rats at doses up to 6 mg/kg/day during organogenesis through delivery and weaning, which is anticipated to be at an exposure close to the MRHD. At 6 mg/kg/day there were reductions in maternal body weight, increased heart weight, a reduction in the viability index in the pups, decreased mean group body weight, suspected dehydration, no milk band present and bent tail. At the NOAEL of 1.5 mg/kg/day there were no maternal effects and no effects in the offspring on sexual maturation, neurobehavioral or reproductive function parameters in the rat offspring. At these doses, no drug-related evidence of teratogenic potential was observed.

Non-clinical Working Patry (NcWP) Response to the CHMP List of Question on aficamten

The EMA NcWP provided input on the potential for reproductive toxicity of aficamten, which is provided here in its entirety:

ICH S5(R3) guideline states that "Clearly positive results for the induction of malformations or embryo-foetal lethality (MEFL), in a single species, at exposures similar to that at the projected clinical exposure at the maximum recommended human dose (MRHD) can be sufficient for risk assessment".

Based on the available data, NcWP agreed that no (visceral) malformations were observed in developmental studies in rats, unlike mavacamten, for which malformations were identified in both species at clinically relevant doses.

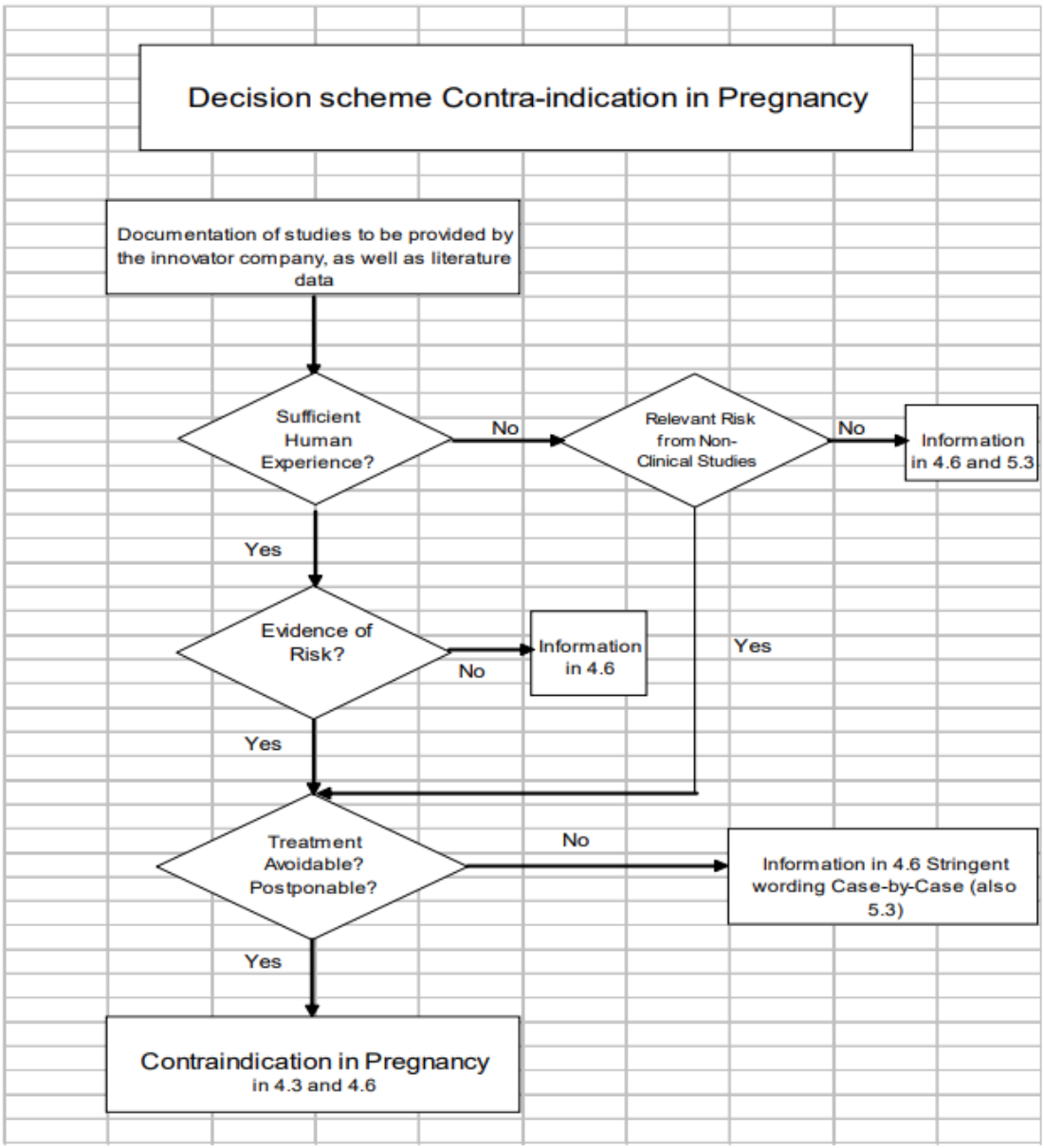
At the LOAEL, in rat EFD and PPND studies, foetal death and decreased pup viability were observed. At this dose (pharmacodynamically driven) maternal toxicity was also present. Given aficamten's primary pharmacology (inhibition of cardiac myosin ATPase activity to reduce hypercontractility in the heart muscle), NcWP considered it plausible that aficamten could exert a direct effect on the developing foetal heart. Therefore, although these findings occurred alongside maternal toxicity, it cannot be excluded that the foetal death and decreased pup viability were induced by the drug's pharmacological action.

In addition, safety margins between the LOAEL, primarily associated with reduced pup viability, and the NOAEL are narrow, with exposures close to those achieved at the MRHD. According to ICHS5(R3) concern increases when the NOAEL occurs at exposures less than 10-fold the human exposure at the MRHD.

In summary, given that some uncertainty remains as to whether the decreased pup viability and foetal deaths result from a direct PD-related effect of aficamten on the foetal heart, the non-clinical findings were considered to represent a relevant risk.

Though several members of NcWP supported the inclusion of stringent wording in the SmPC, along with strong risk minimization measures (e.g., pregnancy testing), and some others advocated for a strict contraindication, there was overall agreement that this decision should not be taken solely based on the non-clinical data.

NcWP therefore recommends that, in line with the flow chart below taken from appendix 2 of the guideline on "risk assessment of medicinal products on human reproduction and lactation: from data to labeling", the decision between a contraindication or stringent wording in Section 4.6 should also involve clinical expertise and consider factors such as the need for uninterrupted maternal treatment during pregnancy, the availability of alternative treatment options, the overall benefit-risk balance, and the feasibility of managing potential risks through strict foetal monitoring and risk minimization measures.



Appendix 2 of GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

Aficamten is considered not to be PBT, nor vPvB. A risk to the STP, surface water, groundwater, sediment, soil and secondary poisoning is not anticipated based on the prescribed use of aficamten.

2.5.7. Conclusion on the non-clinical aspects

In general, the non-clinical pharmacology studies confirmed the proposed mode of action of aficamten. Although binding studies were lacking, functional assays using cardiomyocytes from various species showed inhibition of cell contractility in vitro. Studies in healthy rats, healthy dogs, and the R403Q HCM mouse model showed the potential of aficamten to reduce ventricular contractility in vivo. Furthermore, aficamten has the potential to relieve LVOT obstruction, as demonstrated in the A31P cat

model of oHCM. Together the data provide sufficient proof of concept for the potential of aficamten to alleviate symptoms of oHCM. The potential of aficamten inducing off-target effects on other tissues outside the heart is considered low.

The nonclinical pharmacokinetics of aficamten was shown to be adequately studied in rats when compared to humans, especially with regard to the metabolism, where no unique human major metabolites have been identified.

Animal studies are insufficient with respect to reproductive toxicity. Foetal harm cannot be ruled out based on the mode of action of aficamten.

Aficamten is not genotoxic nor phototoxic. The carcinogenic potential of aficamten is low.

Aficamten is considered not to be PBT, nor vPvB. A risk to the STP, surface water, groundwater, sediment, soil and secondary poisoning is not anticipated based on the prescribed use of aficamten.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A request for GCP inspection was adopted for the following clinical study: CY 6031. Based on the observation and findings identified during the inspections and the character of these findings, it was concluded that the clinical trial was performed in compliance with GCP requirements and that the data obtained, documented and reported are reliable. The trial was conducted in accordance with internally accepted ethical standards.

- **Tabular overview of clinical studies**

Table 2. Clinical studies supporting the clinical pharmacology of aficamten

Study identifier	Study design	Population number of subjects	Formulation / Dosing regimen
Studies in healthy subjects			
6011	Single dose ascending	N=42 aficamten, N=15 placebo	Granules: 1, 3, 10, 25, 40, 50, 75 mg
	Multiple dose ascending	N=18 aficamten, N=6 placebo	Granules: 5, 7.5, 10 mg QD for 14-17 days
	CYP2D6 genetic variants	N=7 poor CYP2D6 metabolisers	Granules: 10 mg
	Food effect	N=12	Granules: 10 mg
	Relative bioavailability	N=12	Granules: 10 mg, Tablets: 10 mg (2x5 mg)
6012	Food effect, PK metabolites	N=18	Tablets: 20 mg (1x20 mg)

6013	Mass balance, PK metabolites	N=8 (males)	Granules: 10 mg
6014	DDI – itraconazole	N=17	Tablets: 10 mg (2x5 mg)
	DDI - carbamazepine	N=17	Tablets: 20 mg (4x5 mg)
	DDI - dabigatran	N=25	Tablets: 20 mg (4x5 mg)
6017	Hepatic impairment, PK metabolites	N=8 moderate hepatic impaired, N=8 subjects with normal hepatic function	Tablets: 20 mg (4x5 mg)
6019	PK metabolites	N=10	Tablets: 50 mg (10x5 mg)
	QTc study	N=34	Tablets: 50 mg (10x5 mg), 400 mg moxifloxacin
601-10	DDI - fluconazole	N=17	Tablets: 10 mg (2x5 mg)
	DDI - paroxetine	N=17	Tablets: 10 mg (2x5 mg)
	DDI - fluoxetine	N=17	Tablets: 10 mg (2x5 mg)
JX01001	Single dose ascending	Chinese N=12 aficamten, N=4 placebo	Tablets: 10 mg, 20 mg (2x5mg, 4x5 mg)
	Multiple dose	N=9 aficamten, N=3 placebo	Tablets: 5 mg
Studies in patients with oHCM			
6021	Dose finding		Echocardiography guided dosing
		N=68 aficamten, N=7 placebo	Start dose 5 mg titration up to 15 mg
		N=14 aficamten, N=7 placebo	Start dose 10 mg titration up to 30 mg
6031	Pivotal placebo controlled	N=142 aficamten, N=140 placebo	Echocardiography guided dosing. Start dose 5 mg titration up to 20 mg.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Aficamten (also known as CK-3773274) is a small molecule, allosteric inhibitor of cardiac myosin as a chronic oral treatment for patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). Aficamten is aimed to reduce the hypercontractility that underlies the pathophysiology of hypertrophic cardiomyopathy by reducing the number of active actin myosin cross-bridges in the cardiac sarcomere.

Aficamten is intended for once daily (QD) oral administration using film-coated tablets at strengths of 5, 10, 15, or 20 mg. The recommended starting dose of aficamten is 5 mg QD, with individualised dose titration in 5 mg increments based on achievement of target LVOT gradients (LVOT-G) and maintenance of normal left ventricular ejection fraction (LVEF) after 2 to 8 weeks of treatment. The maximum recommended dose is 20 mg QD.

Summary of aficamten PK exposure by actual dose received were simulated and results are summarised in Table 6. Most of the subjects were titrated up to 15 mg (N=50) or 20 mg (N=65). Baseline characteristic for the significant covariate sex and bodyweight were equally distributed among the 4 doses. Patients who received higher dose had a higher aficamten PK exposure at steady state.

Table 3. Summary of steady state aficamten exposure by the last titrated dose in patients with oHCM (6031)

	5 mg (N=5)	10 mg (N=22)	15 mg (N=50)	20 mg (N=65)	Overall (N=142)
WT (kg)					
Mean (CV%)	78.6 (28.9%)	75.7 (19.1%)	81.5 (16.9%)	82.8 (20.0%)	81.1 (19.2%)
Median [Min, Max]	69.0 [66.0, 119]	75.5 [55.0, 100]	82.5 [47.0, 125]	80.0 [50.0, 116]	80.0 [47.0, 125]
Sex					
Male	3 (60.0%)	14 (63.6%)	29 (58.0%)	40 (61.5%)	86 (60.6%)
Female	2 (40.0%)	8 (36.4%)	21 (42.0%)	25 (38.5%)	56 (39.4%)
AUCtau (ng.hr/mL)					
Mean (CV%)	2650 (40.9%)	5550 (50.5%)	6410 (31.1%)	7570 (34.4%)	6680 (39.1%)
Median [Min, Max]	2230 [1850, 4540]	4450 [3210, 15700]	5910 [3190, 10900]	7050 [4190, 19200]	6290 [1850, 19200]
Cmax (ng/mL)					
Mean (CV%)	115 (42.4%)	238 (50.4%)	277 (31.8%)	328 (34.5%)	289 (39.5%)
Median [Min, Max]	93.9 [78.0, 199]	192 [137, 673]	254 [136, 508]	302 [179, 813]	274 [78.0, 813]
Ctau (ng/mL)					
Mean (CV%)	102 (43.1%)	212 (54.8%)	241 (34.4%)	281 (37.0%)	250 (41.6%)
Median [Min, Max]	82.4 [70.7, 176]	163 [109, 636]	217 [117, 447]	265 [135, 747]	234 [70.7, 747]

Abbreviations: AUCtau= daily AUC; Cmax= maximum concentration; Ctau=trough concentration; N= number of subjects.
Notes: Exposures were simulated using posthoc PK parameters of the oHCM patients and the last titrated dose in CY 6031.
Source: posthoc.pk.sim.r

Pharmacokinetics of the inactive metabolites M1a and M1b has been measured alongside the pharmacokinetics of aficamten in most studies. The clinical pharmacology program (Table 5) for aficamten encompasses 8 phase 1 studies in healthy subjects and 2 studies in the target population:

- A SAD/MAD study in healthy subjects (**6011**)
- One mass balance, and metabolism study (**6013**)

- Two biopharmaceutical studies investigating relative BE between formulations or food effect (**6011, 6012**)
- Five studies investigating intrinsic factors (**6011**-CYP2D6 poor metabolisers, **6017**-hepatic impairment, JX01001-Chinese healthy subjects) or drug interactions (**6014** - itraconazole, carbamazepine, dabigatran etexilate, **601-10** - fluconazole, paroxetine, fluoxetine)
- One study investigating QTC prolongation (**6019**)
- The dose finding study (**6021**) and pivotal study (**6031**) in oHCM patients

A Population PK analysis was developed (Report **CYT-AFI-PMX-001**) from which predicted exposure metrics were used as input for PKPD and exposure-response (ER) analyses (Report **CYT-AFI-PMX-002**). A physiologically based pharmacokinetic (PBPK) model was developed and applied to a series of simulations to assess drug interaction effects with aficamten as object (Report **CYT/11/B**).

In addition, in vitro studies using human biomaterials were conducted to assess the plasma protein binding, cell permeability, metabolism, and DDI potential of aficamten.

Methods

Bioanalytical analysis

Aficamten, M1a, and M1b were analysed by liquid chromatography-high resolution mass spectrometry, processed by either protein precipitation (plasma) or liquid liquid extraction (urine). Validated bioanalytical methods were used to determine aficamten, and the metabolites M1a and M1b in plasma and urine compliant with the acceptance criteria of the bioanalytical method validation guideline ICH-M10. In study performance of QC plasma samples was in agreement with the validation. All samples were analysed within the established long term stability, ISR samples met acceptance criteria and bioanalytical reports were provided.

PBPK Modeling of Aficamten as the Victim of DDIs (CYT/11/B)
Model development: A top-down PBPK model was developed using minimal physicochemical and nonclinical data, but with the focus of accurately calculating fractional metabolism (fm) by each responsible CYP from observed changes in aficamten AUC∞ after perpetrator drug coadministration in Phase 1 clinical studies (6014 and 601-10).

A PBPK model that includes a simple first order absorption model was developed. Distribution models evaluated included a full PBPK model and a minimal PBPK model, both of which consider liver and intestinal metabolism. Observed apparent oral clearance (CL/F) obtained from healthy subjects following a single oral dose of 10 mg aficamten was used in the model. The CL/F value (3.45 L/h; Clinical Study 601-10, cohort 2, control arm) was used to optimise intrinsic clearance (CLint) values in order to recover the observed aficamten plasma concentration-time profiles. The clinical DDI studies with itraconazole (Clinical Study 6014, cohort 1), paroxetine (Clinical Study 601-10, cohort 2) and fluoxetine (Clinical Study 601-10, cohort 3) were used to assign the relative contribution of CYPs 3A4, 2D6 and 2C19, respectively, to the clearance of aficamten. The remaining metabolism was assigned to CYP2C9. A renal clearance (CLR) value of 0.00263 L/h was used as a direct input to the model (Clinical Study 6013).

Model assumptions: The assumption that all non-CYP3A, 2D6 and 2C19 metabolism was mediated by CYP2C9 was based on overall interpretation of the Phase 1 DDI results where fluconazole (a CYP2C9, CYP2C19, and CYP3A inhibitor) and paroxetine (a CYP2D6 inhibitor) DDIs provide a complete accounting of aficamten metabolism.

The simple first order absorption model limited the PBPK model to metabolism related DDI applications only, no absorption related aspects could be assessed.

Software: Version 22 of the Simcyp Population-Based Simulator (www.simcyp.com) was used for all PBPK modelling and simulation. Substrate and inhibitor, inducer files were provided.

PBPK Model Verification

PBPK estimation of fm based on itraconazole, paroxetine, and fluoxetine DDI data indicates that aficamten, in CYP2C9-NM participants, is primarily eliminated via CYP2C9-mediated metabolism (fm = 50%) with contributions by CYP3A (fm = 26%) and CYP2D6 (fm = 21%). Metabolism via CYP2C19 was estimated to be minimal (fm = 3%).

The accuracy of estimated fm values for CYP2C9, CYP2C19, CYP2D6, and CYP3A was verified by predicting the observed effect of fluconazole (strong CYP2C19, moderate CYP2C9, and moderate CYP3A inhibitor) and carbamazepine (moderate-to-strong CYP3A and weak CYP2C9 inducer) on aficamten exposure. A summary of the of the development and verification data is provided in Table 7.

Table 4. Model development and model verification data (CYT/11/B)

Coadministered Drug	GMR of Aficamten PK Parameter (90% CI)*		simulated aficamten PK parameter		Simulated/observed	
	C_{max}	AUC_{∞}	C_{max}	AUC_{∞}	C_{max}	AUC_{∞}
Development						
Single dose aficamten (601-10)	59.8*	2988*	54.5*	3244*	0.91	1.08
Paroxetine (601-10)	1.20 (1.03, 1.41)	1.27 (1.19, 1.35)	1.02	1.36	0.84	1.08
Itraconazole (6014)	0.93 (0.79, 1.08)	1.26 (1.19, 1.34)	1.01	1.27	1.09	1.01
Fluoxetine (601-10)	1.55 (1.28, 1.88)	1.32 (1.25, 1.40)	1.01	1.29	0.65	0.98
Verification						
Fluconazole (601-10)	0.99 (0.87, 1.13)	3.78 (3.47, 4.11)	1.04	2.49	1.05	0.66
Carbamazepine (6014)	0.69 (0.50, 0.95)	0.49 (0.36, 0.66)	0.96	0.51	1.39	1.03
CYP2D6 normal an intermediate metabolisers (6011)	50*	3043*	47*	3394*	0.93	1.12
CYP2D6 poor metabolisers (6011)	57*	2966*	50*	4349*	0.88	1.47
Multiple dose Accumulation factor (6011)		4.83*		4.82*		1.00

- GMean PK parameter instead of GMR

An updated model including the metabolites M1a and M1b was provided. Plasma concentrations of parent (C_p) were modelled assuming 2-compartment kinetics ($K_{in,p}$ and $K_{out,p}$ to describe distribution into and out of the central compartment [V_p], respectively) with first-order extravascular absorption ($K_{a,p}$) and first-order elimination via three pathways: M1a formation ($K_{f,m1}$), M1b formation ($K_{f,m2}$) and "other" ($K_{e,p}$) was developed to simultaneously model metabolite formation from parent elimination. Plasma concentrations of M1a (C_{m1}) and M1b (C_{m2}) were modelled as 1-compartment kinetics (V_{m1} and V_{m2}, respectively) with first-order elimination ($K_{e,m1}$ and $K_{e,m2}$, respectively). The updated PBPK model showed that elimination rate of the metabolites itself influences the initial concentrations of the metabolites M1a and M1b while the terminal plasma elimination half-life of the metabolites is formation rate-limited.

Observed and predicted values of aficamten, M1a and M1b are shown in Table 7.

Table 5 Observed and simulated AUC_{0-8h} estimates for aficamten and its metabolites with and without perpetrator treatment

Analyte	AUC_{0-8h} (h*ng/mL) Mean (CV%)			
	Observed single dose estimates		**Simulated estimates at steady state**	
	10 mg Aficamten (N=16)	**10 mg Aficamten + 400 mg Fluconazole *QD* (N=16)**	**10 mg Aficamten *QD* (N=16)**	**10 mg Aficamten + 400 mg Fluconazole *QD* (N=16)**
Aficamten	247 (9.92)	281 (14.0)	1050 (15.8)	3750 (22.1)
M1a	123 (36.4)	31.1 (21.8)	719 (30.6)	656 (32.6)
M1b	213 (33.4)	71.8 (28.8)	1320 (23.2)	1510 (21.6)
	10 mg Aficamten (N=17)	**10 mg Aficamten + 40 mg Paroxetine *QD* (N=17)**	**10 mg Aficamten *QD* (N=17)**	**10 mg Aficamten + 40 mg Paroxetine *QD* (N=17)**
Aficamten	250 (23.6)	295 (20.2)	1120 (24.5)	1420 (24.2)
M1a	127 (44.0)	121 (30.8)	887 (26.4)	945 (26.6)
M1b	246 (48.3)	189 (33.8)	1610 (31.4)	1420 (26.2)
	10 mg Aficamten (N=16)	**10 mg Aficamten + 40 mg Fluoxetine *QD* (N=16)**	**10 mg Aficamten *QD (*N=16*)***	**10 mg Aficamten + 40 mg Fluoxetine *QD* (N=16)**
Aficamten	268 (22.8)	307 (18.9)	1170 (20.4)	1540 (21.5)
M1a	122 (28.8)	125 (26.5)	852 (28.9)	917 (24.6)
M1b	208 (27.5)	226 (25.7)	1370 (15.6)	1520 (15.5)
	10 mg Aficamten (N=17)	**10 mg Aficamten + 200 mg Itraconazole *QD* (N=17)**	**10 mg Aficamten *QD* (N=17)**	**10 mg Aficamten + 200 mg Itraconazole *QD* (N=17)**
Aficamten	235 (24.6)	249 (29.5)	1250 (27.1)	1480 (37.4)
M1a	105 (23.8)	124 (37.8)	829 (22.4)	1070 (35.1)
M1b	174 (26.4)	206 (37.1)	1280 (23.6)	1500 (28.3)
	10 mg Aficamten (N=17)	**10 mg Aficamten + 300 mg Carbamazepine BID (N=15)**	**10 mg Aficamten *QD* (N=17)**	**10 mg Aficamten + 300 mg Carbamazepine *BID* (N=15)**
Aficamten	477 (13.1)	406 (33.7)	1180 (26.4)	676 (34.5)
M1a	191 (24.9)	248 (42.1)	1340 (29.4)	1080 (37.8)
M1b	341 (20.6)	469 (40.7)	2500 (16.0)	2070 (33.2)

AUC = area under the concentration-time curve; AUC_{0-8} = AUC from time 0 to 8 hours postdose; CV = coefficient of variation; N = number of participants; QD = once daily.
Note: Arithmetic mean (%CV) are presented.

Population PK modelling (CYT-AFI-PMX-001)

The popPK analysis contained 447 subjects (264 healthy participants and 183 patients with oHCM) and a total of 9963 observations. Summary of baseline demographic covariates by population are

presented in Table 8. There were 13 subjects > 75 years of age, 59 65-<75 years, and 111 < 65 years in the popPK analysis.

Table 6 Summary of demographics covariates in the popPK dataset

	Healthy participant (N=264)	oHCM (N=183)	Overall (N=447)
Age (yr)			
Median [Min, Max]	36.0 [18.0, 64.0]	59.0 [18.0, 83.0]	43.0 [18.0, 83.0]
Weight (kg)			
Median [Min, Max]	74.5 [48.2, 108]	80.0 [47.0, 156]	77.2 [47.0, 156]
BMI (kg/m2)			
Median [Min, Max]	26.1 [18.3, 37.6]	28.5 [18.4, 48.4]	27.0 [18.3, 48.4]
Sex			
Female	98 (37.1%)	78 (42.6%)	176 (39.4%)
Male	166 (62.9%)	105 (57.4%)	271 (60.6%)
Race			
White	171 (64.8%)	147 (80.3%)	318 (71.1%)
Black of African American	46 (17.4%)	4 (2.2%)	50 (11.2%)
Asian	30 (11.4%)	30 (16.4%)	60 (13.4%)
American Indian or Alaskan Native	4 (1.5%)	0 (0%)	4 (0.9%)
Native Hawaiian or other Pacific islander	1 (0.4%)	0 (0%)	1 (0.2%)
Multiple	11 (4.2%)	0 (0%)	11 (2.5%)
Other	1 (0.4%)	2 (1.1%)	3 (0.7%)

The final popPK model was a 2-compartment model with linear elimination of aficamten. Absorption of aficamten was modelled as first order after a lag time (Table 9). Besides body weight on volume (Vc/F and Vp/F) and clearance (CL/F and Q/F), significant covariates in the final PopPK model include population (healthy participants versus participants with oHCM) and sex on CL/F and Vp/F, formulation (encapsulated granules versus tablet) on Tlag, and food status on bioavailability (F1), Tlag, and Ka.

Table 7. Population parameter estimates for the final popPK model

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)
CL/F	L/hr	2.62	2.53	
Vc/F	L	18.1	12.6	
Q/F	L/hr	57.6	1.14	
Vp/F	L	295	4.37	
Ka	1/hr	0.337	5.03	
Tlag of Tablets	Hr	0.229	0.17	
Tlag of Capsule	Hr	0.248	0.0268	
Fasted on Ka		0.170	47	
WT on CL and Q		0.586	8.02	
WT on Vc and Vp		0.882	13.1	
Healthy Participants on CL		0.356	12.1	
Sex Female on CL		-0.128	22	
Healthy Participants on Vp		0.266	22.5	
Sex Female on Vp		-0.193	14.4	
High fat meal on Tlag		0.115	2.12	
High fat meal on F1		0.0687	17.1	
High fat meal on Ka		-0.365	12.3	
IIV (%CV)				
ω^2_CL/F		0.0793 (28.7%)	6.4	6.9
ω^2_Vc/F		2.35 (308%)	11.9	22.6
ω^2_Vp/F		0.041 (20.5%)	12.9	28.7
ω^2_Ka		0.329 (62.4%)	9.77	17.2
Residual Error (%CV)				
δ^2 (log-additive)		0.0414 (20.3%)	0.571	6.5

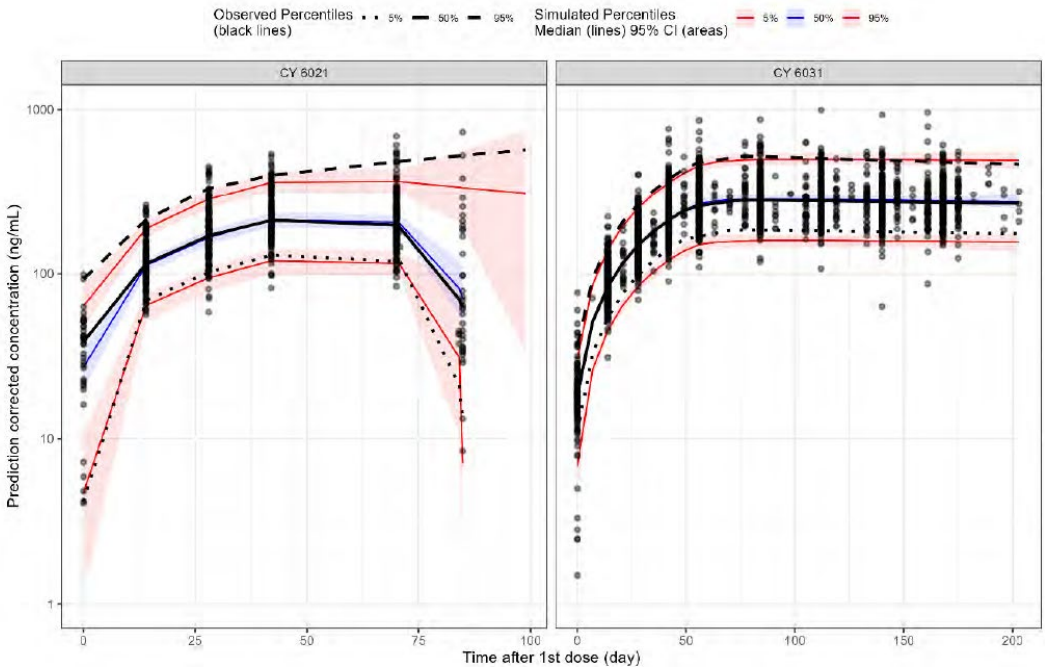
Abbreviations: CL/F= apparent clearance; F= oral bioavailability; IIV = interindividual variability; KA = first order absorption rate; PPK = population pharmacokinetics; Q/F = apparent intercompartmental clearance; RSE = relative standard error; Tlag = absorption lag time; Vc/F = apparent volume of the central compartment; Vp/F = apparent volume of the peripheral compartment; WT= weight.

Notes: IIV was reported as variance (ω^2) and %CV (sqrt(exp(ω^2) – 1) x 100 (%)); RSE calculated as standard error/estimate x 100 (%).

Source: final.pk.model.r

The GOF plots showed good agreement between the individual or population predicted aficamten concentrations and the observed concentrations. CWRES were uniformly distributed around 0 over the range time after last dose and predicted concentrations. Also the pcVPC showed adequate predictions of the median prediction but also for the 95% and 5% percentiles in subjects with oHCM (Figure 2).

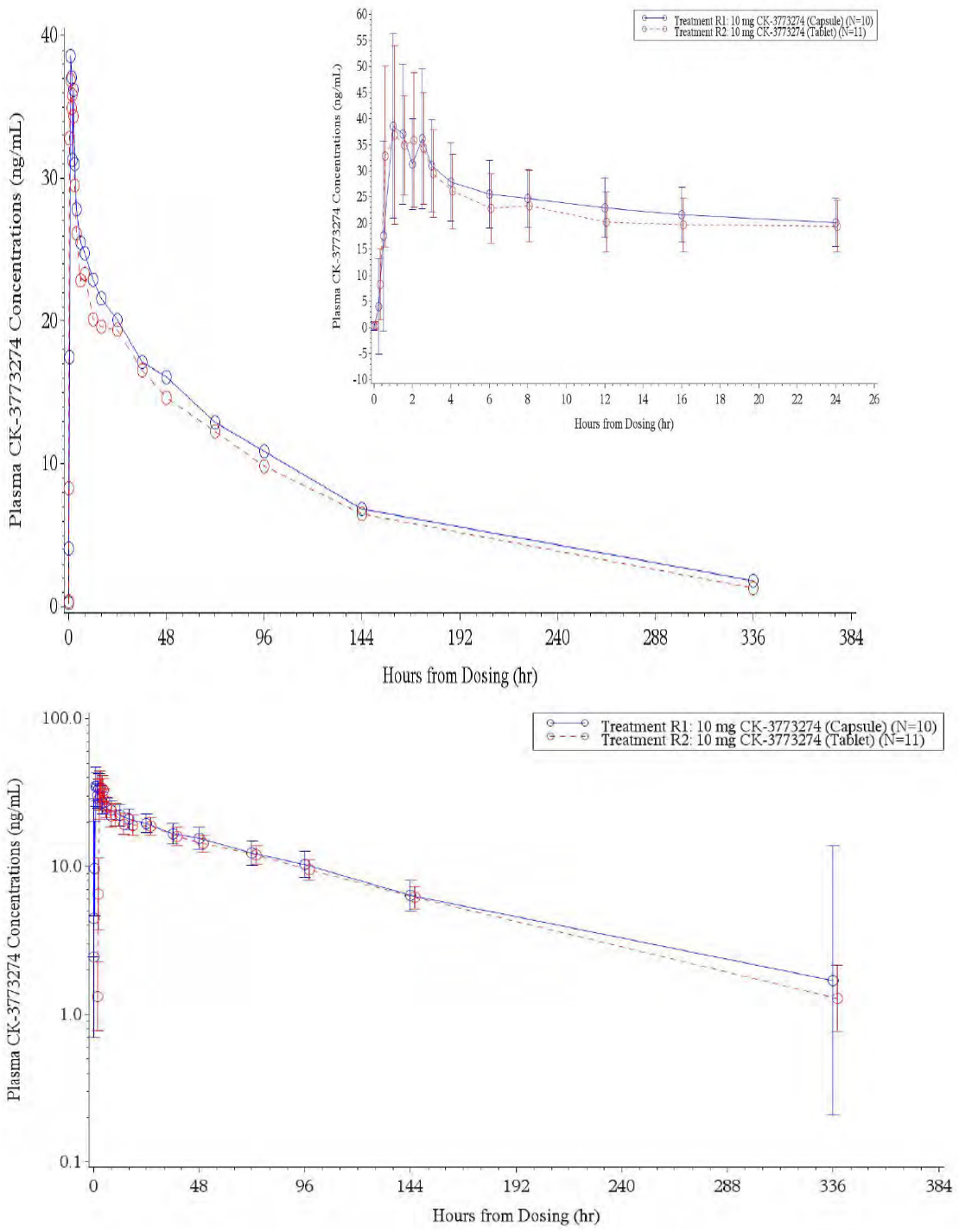
Figure 2. pcVPC versus time in patients with oHCM for final popPK model



Absorption

Following oral administration of aficamten median aficamten tmax ranged from approximately 1 to 2 hours postdose across various doses. Aficamten concentrations declined in a biphasic manner with median t½ of approximately 80 hours (Figure 3). Aficamten mean Cmax was 119 ng/mL and AUC0-inf 5910 ng.h/mL at a 20 mg single dose with the commercial tablets in healthy subjects (Study 6012). 20 mg dose at steady-state in subjects with oHCM (Study 6031) resulted in an aficamten mean Cmax of 328 ng/mL and AUCtau of 7050 ng.h/mL.

Figure 3. Mean (SD) Plasma aficamten concentration-time profiles following a single oral dose of 10 mg aficamten granules in a capsule and a tablet (study 6011, Part 5, linear and log-linear plots, insert plasma concentrations first 24h)



The solubility of aficamten was characterized as required. The apparent permeability (Papp) of aficamten in Caco-2 cells was estimated.

Absolute bioavailability was not evaluated.

Effect of a high fat meal on the absorption of aficamten has been evaluated for 20 mg commercial tablet formulation (study 6012) and 10 mg encapsulated granules (study 6011). No effect on the extent of absorption of aficamten was observed, while for the tablets a 15% reduction in Cmax was

observed after a high fat meal. In the phase 2 and phase 3 studies aficamten could be taken with or without a meal.

Three formulations have been used during clinical development: encapsulated granules were used for single and multiple dose ascending study 6011, for all other studies and purposes a tablet formulation has been used. For the phase 2 studies the tablet formulation was a % w/w while for the other studies including the phase 3 study a tablet () was used. The commercial formulation is a film coated tablet with 4 strengths 5, 10, 15, and 20 mg. The 20 mg commercial formulation has been used in study 6012. Effect of formulation on the bioavailability of aficamten was compared for the granules capsules and the phase 2 tablets in a randomised, 2-way crossover design in study 6011. Aficamten bioavailability was similar for the encapsulated granules and the tablets since rate and extent of absorption of aficamten were within the 90% CI of 80-125%.

Distribution

Plasma protein binding of aficamten in humans is approximately 90% for aficamten, M1a, and M1b as determined by equilibrium dialysis (Nonclin-0017, Nonclin-0249, and Nonclin-0124). No concentration dependency of plasma protein binding was observed.

Ex vivo protein binding in healthy subjects was fu=0.06 (study 6017). No differences in plasma protein binding of aficamten was observed between clinical study samples from participants with normal hepatic function and moderate hepatic impairment.

Whole blood to-plasma ratio was approximately 0.9, 0.8, and 0.7 across concentration levels for aficamten, M1a, and M1bCK, respectively (Nonclin-0032 and Nonclin-0201). No concentration dependency of partitioning was observed. In the mass balance study, blood to plasma total radioactivity ratio was 0.6 (study 6013).

Apparent volume of distribution of aficamten is 309L in participants with oHCM (popPK modelling).

Elimination

Across the clinical studies in healthy subjects, mean elimination half-life of aficamten, M1a, and M1b was approximately 80 hours. Apparent clearance ranged from 2.9-4.5 L/h, whereas renal clearance amounted 2.6 mL/h. Subjects with oHCM had a similar elimination half-life as healthy subjects but the apparent clearance was approximately 25% lower approximately 2.6 L/h.

In the mass balance study 6013, faeces was the primary route of excretion and accounted for 57.7% of total radioactivity, while urine accounted for 32.0% of total radioactivity. The overall mean recovery of total radioactivity in urine and faeces was 89.7%.

Urine recovery of aficamten was low, representing 0.055% of the administered dose. 12 metabolites were detected and quantitated in pooled urine samples. The most abundant metabolites in urine, albeit minor (<10% of dose), were M1a/M1b and M5, accounting for 9.4% and 8.0% of the dose, respectively.

Aficamten accounted for a minor proportion of radioactivity in faeces (5.1% of the dose), while M18 was the major species in faeces and accounted for 44.1% of the dose. The other 4 metabolites amounted each 0.25-2.7% of the administered dose.

In plasma (Table 10), the most abundant circulating components were aficamten, M1a, and M1b, which accounted for 29.0%, 17.1%, and 31.3% respectively, of total circulating radioactivity. Using pooled plasma samples three more metabolites were identified: M3 (<1.5%), not further identified, M5

(10.3%) a glucuronide of M1a/M1b, and M64 (<1.5%) a sulfate of M1a/M1b. The stereoisomers M1a and M1b are not pharmacologically active (Nonclin-0460).

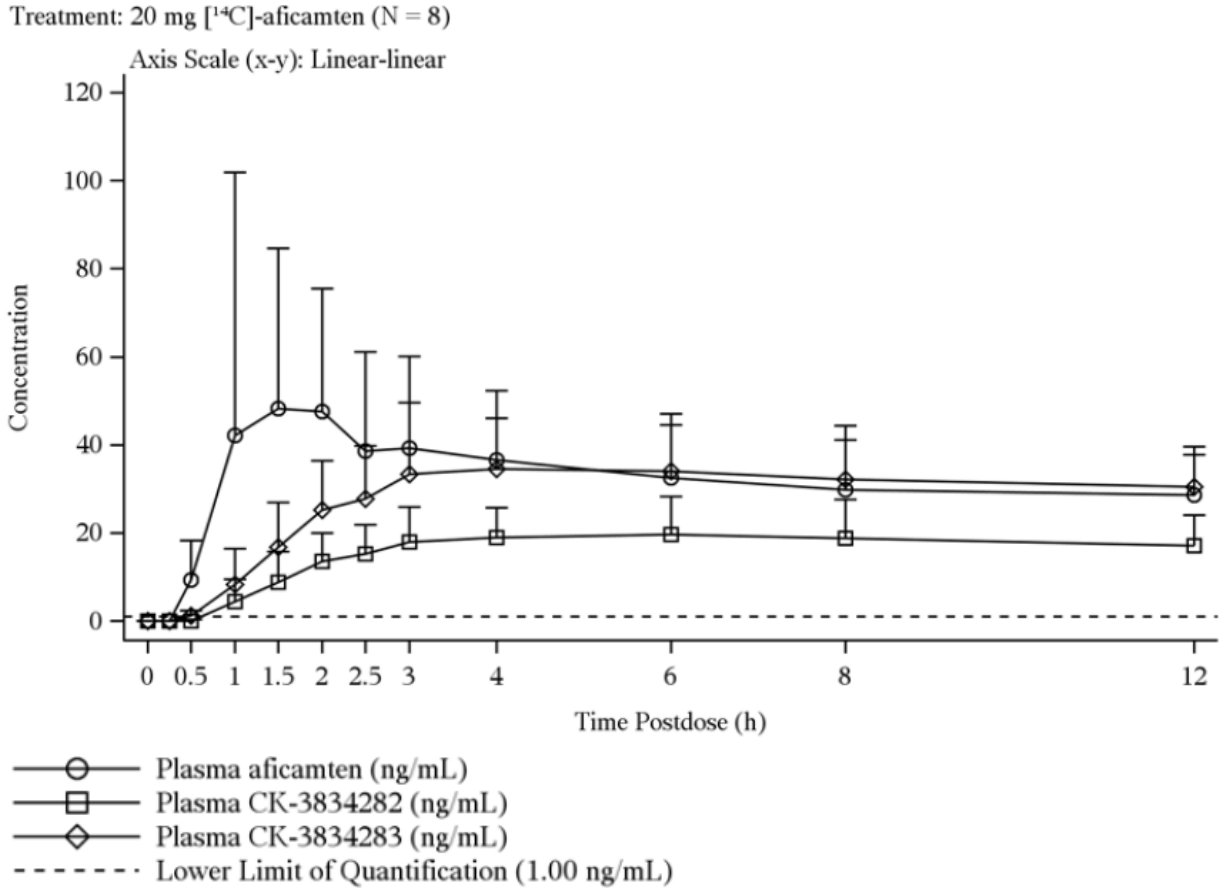
Table 8. Summary of Plasma Pharmacokinetic Parameters for Aficamten, CK-3834282, CK-3834283, and Total Radioactivity Following a Single Oral Dose of 20 mg ^{14}C-Aficamten in Healthy Male Participants (Study 6013)

Analyte	Geometric Mean (CV%) [n][a]						
	C_{max} (ng/mL)	**t_{max} (h)**	**AUC_t (ng·h/mL)**	**AUC_∞ (ng·h/mL)**	**CL/F (L/h)**	**V_z/F (L)**	**$t_{½}$ (h)**
Aficamten	61.8 (56.8) [n = 8]	2.00 [1.00, 6.00] [n = 8]	4120 (31.5) [n = 8]	4440 (31.8) [n = 8]	4.50 (32.1) [n = 8]	690 (35.0) [n = 8]	99.6 [81.5, 209] [n = 8]
M1a (CK-3834282)	23.8 (31.1) [n = 8]	5.00 [3.00, 36.0] [n = 8]	2380 (61.7) [n = 8]	2610 (52.7) [n = 8]	NC	NC	94.8 [76.8, 208] [n = 8]
M1b (CK-3834283)	42.3 (29.3) [n = 8]	5.00 [3.00, 36.0] [n = 8]	4590 (32.6) [n = 8]	4790 (31.5) [n = 8]	NC	NC	95.4 [77.6, 180] [n = 8]
Total Radioactivity[b]	111 (43.2) [n = 8]	3.50 [1.00, 6.00] [n = 8]	13700 (28.8) [n = 8]	15300 (26.0) [n = 8]	NC	NC	98.2 [80.1, 230] [n = 8]
Whole Blood Total Radioactivity	66.7 (44.9) [n = 8]	4.50 [1.00, 16.0] [n = 8]	5710 (38.5) [n = 8]	8660 (23.7) [n = 8]	NC	NC	100 [86.2, 171] [n = 8]

AUC = area under the concentration-time curve; AUC_∞ = AUC from time 0 extrapolated to infinity; AUC_t = AUC from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; C_{max} = maximum concentration; CV% = percent coefficient of variation; n = number with estimable parameter; NC = not calculated; $t_{½}$ = terminal elimination half-life; t_{max} = time to maximum concentration; V_z/F = apparent volume of distribution.
Source: Study CY 6013 CSR Table 14.2.1.2

Formation of metabolites M1a and M1b was steady with Cmax observed 3 hours later than aficamten (median time to maximum concentration [tmax] 5.00 versus 2.00 hours postdose) (Figure 4). The median t½ of aficamten was similar to the elimination half-life for the metabolites (Table 10).

Figure 4. Plasma concentrations of aficamten and metabolites M1a (CK-3834282) and M1b (CK-3834283) following administration of 20 mg ^{14}C-aficamten (study 6013)



Aficamten is primarily metabolised by oxidation and reduction, with secondary pathways of glucuronidation, hydrolysis, and sulfonation. The major metabolic pathway is hydroxylation to metabolites M1a and M1b, followed by further biotransformation to M5, M18, and other metabolites.

Metabolite to parent ratio in oHCM patients was 0.70 and 1.03 for M1a and M1b, respectively.

In human microsomes, aficamten degradation was minimal in 120 min but evaluation the formation of M1 revealed that multiple enzymes (CYP2D6, 2C9, 2C8, 2C19 and 3A4) were able to be involved in the formation of M1a/M1b.

Dose proportionality and time dependencies

Dose proportional pharmacokinetics was evaluated in the SAD/MAD study 6011 using the encapsulated granules over a dose range of 1-75 mg, and in a pooled across study comparison (Studies 6014, 601-10, 6012, 6017, and 6019) over the dose range 10-50 mg using the phase 3/commercial tablet formulation. The PK of aficamten was generally linear and systemic exposure increased proportionally over the dose range of 3 to 50 mg.

Consistent with the estimated t½, the mean accumulation ratio for aficamten based on AUC ranged from approximately 4.6 to 4.9 with QD dosing. Metabolite to parent ratio was similar for M1a (0.73)

and M1b (1.31) following single dose and at steady-state. Hence, pharmacokinetics of aficamten were not time-dependent.

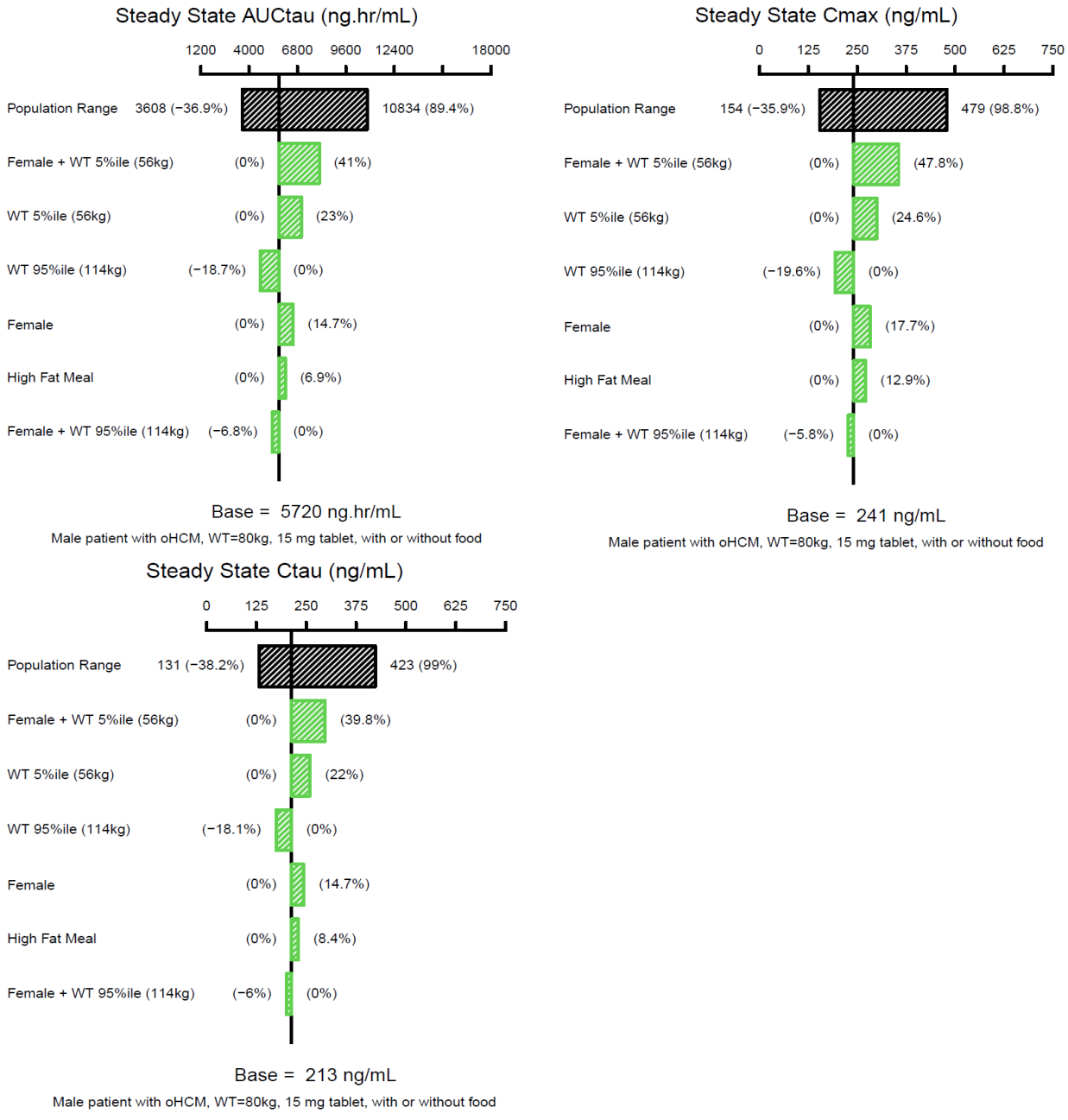
Based on Ctrough levels in the MAD study 6011, steady-state was reached after 2 to 3 weeks.

Special populations

Impact of intrinsic factors is evaluated by popPK analysis (CYT AFI PMX 001) and in study 6017 in subjects with moderate hepatic impairment. Influence of covariates on aficamten PK is illustrated in Figure 5, where the isolated impact of each covariate on plasma aficamten exposure at steady-state following 15 mg aficamten (median last stable dose in 6031) QD dosing were calculated.

Body weight and sex were both found to be significant covariates on volume and clearance parameters of aficamten in PopPK analysis. Age, ethnic factors, renal function were no significant covariates. Females had on average a 15% higher aficamten exposure compared to males with the same bodyweight. However, as females have on average a lower bodyweight, aficamten exposure was on average 30% higher in females compared to males. Aficamten plasma exposure is approximately 40% higher in subjects with the 5% low body weight compared to subjects with 95% highest body weight. Other model-determined significant covariates (formulation and food status) demonstrated no-to-minimal impact on steady-state aficamten exposures. Overall, the isolated impact of covariates on steady-state aficamten exposure is predicted to be <25%.

Figure 5. Population PK-predicted Isolated Impact of Covariates on Steady-state Aficamten Plasma Exposures in Participants with oHCM



AUC_{tau} = area under the concentration-time curve over the dosing interval; C_{max} = maximum concentration; C_{tau} = trough concentration; oHCM = obstructive hypertrophic cardiomyopathy; PK = pharmacokinetic; WT = body weight.
Note: Black bar represents 5th to 95th percentile of the exposure calculated using empirical Bayes estimates of the oHCM population for a dose regimen of 15 mg tablet once daily (median last stable dose in CY 6031) with or without food. The impact of a covariate on the exposure was calculated using the parameter(s) incorporating the isolated effect of that covariate, with other unaffected parameters fixed to the typical values (estimated for a male participant with oHCM with baseline body weight of 80 kg). Baseline body weight was evaluated at the 5th to 95th percentile of the population.
Source: CYT-AFI-PMX-001 Figure 5.8, Figure 5.9, and Figure 5.10

In study 6017, impact of hepatic function on the pharmacokinetics of aficamten was evaluated. AUC values of aficamten, M1a, and M1b following a single dose of 20 mg aficamten were similar in

participants with normal hepatic function and participants with liver cirrhosis and moderate hepatic impairment (Child-Pugh Class B). Protein binding (fu=0.06) was similar in subjects with hepatic impairment and matched control.

Aficamten exposure was 35% higher in subjects > 75 years (13/183) compared to subjects < 65 years of age (111/183). This is likely due to the decreased body weight and increased proportion of female participants with increasing age group in the dataset. Age was no covariate in the popPK model.

In study 6011, the effect of CYP2D6 genetic variants on the PK of aficamten was evaluated. AUCt and Cmax were numerically higher (9% and 18%, respectively) in PM phenotype relative to normal metaboliser (NM)-phenotype participants.

Aficamten PK in healthy Chinese participants was similar to that observed in other Phase 1 studies in the Caucasian population (JX01001).

Pharmacokinetic interaction studies

Two interaction studies (6014, 601-10) were conducted to evaluate effect of CYP2C9, CYP2C19, CYPD6, and CYP3A4 inhibitors and inducer on the pharmacokinetics of aficamten and metabolites M1a and M1b. The results are summarised in Table 11. Itraconazole increased the AUC of aficamten by 25% without affecting Cmax while paroxetine and fluoxetine increased the Cmax and AUC of aficamten with 20-50%. Fluconazole largely increased the AUC of aficamten, 3.8-fold increase, which was accompanied by a 3-fold increase in elimination half-life. Carbamazepine a moderate to strong inducer, decreased Cmax and AUC of aficamten with 37% and 50%, respectively, accompanied by a shorter elimination half-life.

In vitro interaction studies indicated that the potential for clinically relevant inhibition of P-gp by aficamten could not be excluded. Therefore, the effect of aficamten on the PK dabigatran was evaluated (study 6014). Aficamten increased the AUC and Cmax of dabigatran with 25%.

Table 9. Observed effect of coadministered drugs on the PK of aficamten and metabolites M1a and M1b in healthy participants (Studies CY 6014 and CY 601-10)

Coadministered Drug	Dose Regimen of Coadministered Drug	GMR of Aficamten PK Parameter (90% CI)[a]		GMR of M1a PK Parameter (90% CI)[a]		GMR of M1b PK Parameter (90% CI)[a]	
		C_{max}	AUC_{∞}	C_{max}	AUC_{∞}	C_{max}	AUC_{∞}
Strong CYP2D6 Inhibitor: Paroxetine (N = 17)	20 mg QD × 7 days + 40 mg QD × 18 days	1.20 (1.03, 1.41)	1.27 (1.19, 1.35)	0.97 (0.90, 1.05)	1.08 (1.03, 1.13)	0.79 (0.72, 0.86)	0.90 (0.87, 0.94)
Strong CYP3A Inhibitor: Itraconazole (N = 16)[b]	200 mg QD × 12 days	0.93 (0.79, 1.08)	1.26 (1.19, 1.34)	1.05 (0.88, 125)	1.20 (1.02, 141)	1.05 (0.91, 123)	1.11 (0.93, 1.34)
Strong CYP2C19, Moderate CYP2C9, and Moderate CYP3A Inhibitor: Fluconazole (N = 16)	400 mg QD × 18 days	0.99 (0.87, 1.13)	3.78 (3.47, 4.11)	0.27 (0.25, 0.30)	0.92 (0.84, 1.01)	0.35 (0.32, 0.38)	1.12 (1.09, 1.22)
Strong CYP2C19 and Strong CYP2D6 Inhibitor: Fluoxetine (N = 16)	20 mg QD × 7 days + 40 mg QD × 20 days	1.55 (1.28, 1.88)	1.32 (1.25, 1.40)	0.98 (0.88, 1.11)	1.08 (1.02, 1.14)	1.05 (0.96, 1.15)	1.10 (1.06, 1.15)
Moderate-to-Strong CYP3A and Weak CYP2C9 Inducer: Carbamazepine (N = 15-17)	100 mg BID × 3 days + 200 mg BID × 4 days + 300 mg BID × 20 days	0.69 (0.50, 0.95)	0.49 (0.36, 0.66)	1.10 (0.84, 145)	0.62 (0.38, 100)	1.14 (0.85, 1.54)	0.72 (0.53, 0.98)

AUC_{∞} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; BID = twice daily; CI = confidence interval; C_{max} = maximum observed plasma concentration; CYP = cytochrome P450; GMR = geometric least-squares mean ratio; N = number with estimable parameter; PK = pharmacokinetics; QD = once daily.

To further understand the effects of CYP2C9, CYP2C19, CYP2D6, and CYP3A inhibition and CYP2C9, CYP2C19, and CYP3A induction on the PK of aficamten, a PBPK model was developed (method section) to supplement the Phase 1 clinical DDI program and provide a comprehensive evaluation of aficamten DDI liability as a victim drug.

Since CYP2C9 appears to be the predominant enzyme in the elimination of aficamten, the PBPK model-predicted effects of DDI perpetrator drug coadministration on aficamten AUC∞ are presented by CYP2C9 metabolizer phenotype. It is important to note that, as expected from the low hepatic extraction for aficamten, the PBPK model could not predict a material increase in aficamten Cmax after any inhibitor coadministration (CYT/11/B). As such, only changes in aficamten AUC∞ are further summarized (Table 12). Dose recommendations based on these predictions are also summarised in the table.

Table 10. Observed DDI effects and PBPK-predicted effect of coadministered drugs on the PK of aficamten in healthy participants (CYT/11/B)

Coadministered Drug	**Dose Regimen of Coadministered Drug**	**CYP2C9 Phenotype**	**Fold change Aficamten AUC_{∞} GMR (90% CI)[c]**	**SmPC** **dosing proposal for patients stable on aficamten dosing without co-medications**
Strong CYP2C9 Inhibitor: Sulfaphenazole	2000 mg QD	NM	2.1	Avoid concomitant administration (see section 4.2)
Strong CYP2C19, Moderate CYP3A, and Moderate CYP2C9 Inhibitor: fluconazole	400 mg QD	NM	3.7	More than a single dose of fluconazole coadministration is contra-indicated (see section 4.3).
Strong CYP2D6 Inhibitor: Paroxetine	40 mg QD	PM	1.4	Normal dosing
Strong CYP3A Inhibitor: Itraconazole	200 mg QD	NM	1.3	Normal dosing
		PM	1.5	
Moderate CYP2D6 Inhibitor: Duloxetine	60 mg BID	PM	1.2	Normal dosing
Moderate CYP3A Inhibitor: Verapamil	80 mg TID	PM	1.4	Normal dosing
Strong CYP2C19, Moderate CYP3A, and Moderate CYP2C9 Inhibitor: Fluconazole	Intermittent dosing: 2 × 150 mg, separated by 48 hours	NM	1.1	Coadministration is contraindicated for more than a single dose of fluconazole (see section 4.3).
		PM	1.1	

Strong CYP2D6 and CYP2C19 Inhibitor: Fluoxetine	40 mg QD	NM	1.2	Normal dosing
		PM	1.3	
	60 mg QD	NM	1.2	
		PM	1.3	
Strong CYP2C19, Weak-to-Moderate CYP3A4, Weak CYP2C9, and Weak CYP2D6 inhibitor: Fluvoxamine	150 mg BID	NM	2.2	Reduce dose of aficamten from 20 mg to 10 mg, 15 mg to 5 mg in patients who intend to initiate fluvoxamine or voriconazole. Avoid if on 10 mg or 5 mg aficamten. Maximal aficamten dose is 15 mg (see section 4.2, 4.5) Assess LVEF and LVOT-G after inhibitor initiation and dose titrate according to Table 1.
		PM	1.9	
Strong CYP3A4, Moderate CYP2C19, and Weak CYP2C9 inhibitor: Voriconazole	200 mg BID	NM	1.9	
		PM	2.2	
Strong CYP3A, Strong CYP2C19, and Moderate CYP2C9 inducer: Rifampin	600 mg QD	NM	0.2	contraindication
		PM	0.2	
		PM	0.6	

Pharmacokinetics using human biomaterials

The in vitro drug interaction potential of aficamten, metabolites M1a and M1b has been investigated for CYP enzymes and transporters (studies Nonclin-0033, Nonclin-0052, Nonclin-0126, Nonclin-016, Nonclin-0123, Nonclin-0009, Nonclin 0008, Nonclin 0127, and Nonclin-0169).

Aficamten and metabolites M1a and M1b were no inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.

Aficamten induced CYP1A2 dose dependently in 1 batch with 2.9-fold increase at 50 µM an 2-fold increase at 25µM. In 2 batches, CYP3A4 was induced 2-fold at 25 µM with a maximum of 3.2 µM at 50 µM. Aficamten did not induce CYP2B6.

Metabolites M1a and M1b did not induce CYP2B6 or 3A4 but potentially induced CYP1A2 in 2 hepatocyte batches with a 2-fold increase at 25, 100 and 2.8 µM, 100µM, respectively, with maximal induction of 2.9 and 3.5 at 100 µM.

Aficamten was not a substrate of breast cancer resistance protein (BCRP), P-gp, organic anion transporting polypeptide (OATP)1B1, or OATP1B3. Aficamten its metabolites M1a and M1b did not inhibit BCRP, OCT2, OCT3, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, and MATE2-K. The potential for clinically relevant inhibition of P-gp by aficamten could not be excluded.

2.6.2.2. Pharmacodynamics

Mechanism of action

Aficamten (CK-3773274) is a small-molecule, allosteric inhibitor of cardiac myosin. The reduction in cardiac contractile force alleviates left ventricular outflow tract (LVOT) obstruction in patients with oHCM by mitigating mitral valve systolic anterior motion and septal contact, thus improving functional capacity and alleviating symptoms. Clinical data supporting the mechanisms of action comes from the PD effects found across studies, including reductions in LVOT-G and LVEF.

Primary and Secondary pharmacology

The primary and secondary pharmacology studies consist of the first-in-human trial CY-6011 evaluating the dose response on LVEF reduction, a dedicated QTc study CY 6019 and a PK/PD modelling and exposure response analyses report.

CY-6011

In the single ascending dose part of study 6011 in healthy subjects, doses 1, 3, 10, 25, 40, 50, 75 mg, at least 5% reductions in LVEF occurred in the single doses of 40 mg and above, reaching stopping criteria at 75 mg aficamten. LVEF changes from baseline were statistically significantly different from placebo in the single dose 50 mg aficamten group at all time points (Day 1 Hours 1.5, 4, 6, and 24), which appeared to have greater decreases from baseline compared to placebo (LS Mean Difference: -5.511% – -2.350%; p-value: 0.0001 – 0.0213), and for single dose 40 mg at Day 1 Hour 1.5, which also appeared to have greater decreases from baseline compared to placebo (LS Mean Difference: -3.448%; p-value: 0.0384). There were no statistically significant differences in the single dose 1, 3, 10, or 25 mg treatment groups at any time point. Of note, the single dose 50 mg group included 11 subjects, while single dose 1, 3, 10, 25, and 40 mg groups included 6 subjects each, which may have resulted in better precision of statistical comparisons for the 50 mg group. There appeared to be a statistically significant effect of plasma aficamten concentration on LVEF change from baseline (Slope Estimate: -0.0145; p-value: 0.0027), see Figure 6.

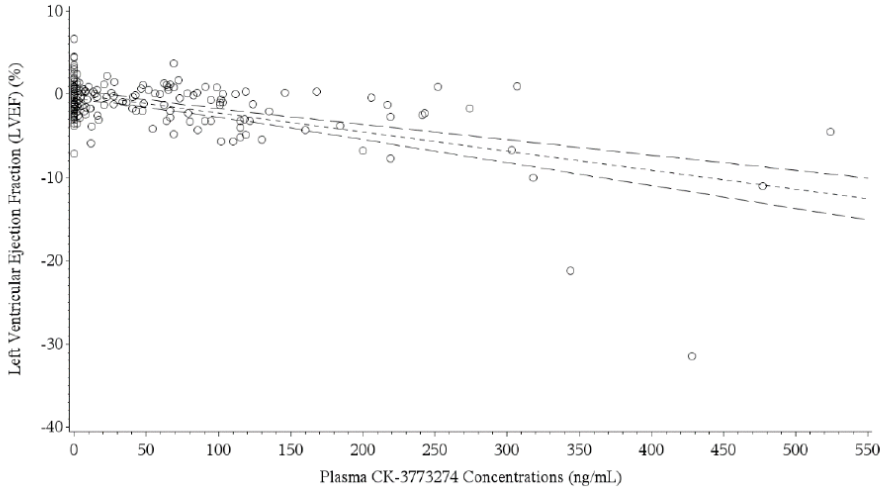


Figure 6. Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Versus Time-Matched Plasma aficamten (CK-3773274) Concentrations

In the multiple ascending dose (5, 7.5, 10 mg) part of the study, the greatest decreases occurred in the 10 mg aficamten group (minimum mean change of -5.02% at Day 14 Hour 1.5).

QTc prolongation

Preliminary concentration-QT (C-QT) effect modeling in the single-dose portion of CY 6011 using a simple linear regression demonstrated a slightly negative slope (p-value = 0.4) with an intercept of -1.6 msec, suggesting that aficamten has no effect on QTc. Concentration-QT effect modeling results were similar in the multiple-dose portion of the study in that the slope was negative. Similarly, the ECG evaluation in the Phase 2 study (CY 6021) demonstrated no evidence of QTc prolongation. Nonetheless, to exclude an effect on QTc prolongation, the Applicant has conducted a thorough QT study in healthy participants, CY 6019.

CY 6019

The QT-study was conducted using a single oral dose of 50 mg aficamten (10 × 5 mg tablets), or 400 mg moxifloxacin as positive control. A 50 mg dose was selected for aficamten since after a 50 mg single dose, aficamten and its metabolites achieved generally comparable exposure to 15 mg QD dosing in patients with oHCM at steady state (CY 6031). Assay sensitivity was established by the lower bound of 90% CI for moxifloxacin exceeding 5 msec using C-QT and by time points analyses.

A total of 5 C-QT models were explored: the models with each analyte alone and the models with a combination of the parent with each metabolite (aficamten + CK-3834282 and aficamten + CK-3834283). The model with t-value < 1.95 and the smallest AIC estimate was selected as the primary model. All 5 models were comparable with t-values < 1.95 and similar AIC values (range: 3966.7 to 4011.9). The model with metabolite CK-3834283 alone had the smallest AIC (AIC = 3966.7) and was therefore selected as the primary model. Since the primary objective of this study was to assess the effect of aficamten on QTc interval, the next best model that included aficamten and CK-3834282 was chosen as the secondary model to allow cardiodynamic evaluation of all analytes.

The predicted ddQTcF values were comparable across all tested models. The upper bound of the 90% CI of predicted ddQTcF for aficamten (-0.214 msec; secondary model), CK-3834282 (0.088 msec, secondary model), and CK-3834283 (0.145 msec, primary model) were all less than 10 msec, thereby confirming lack of QTc prolongation by aficamten and its metabolites. The estimated slope of the C-QT

relationship for aficamten was negative but not statistically significant (-0.00198 msec per ng/mL [90% CI: -0.00908, 0.00512]). Similar results were obtained for the other models.

The hysteresis assessment and loop plots also indicate lack of hysteresis for aficamten and its metabolites in this study. Following all treatments, mean QTcF values remained within the normal limits (< 450 msec), as observed in healthy adults.

Pharmacodynamic interactions with other medicinal products or substances

No dedicated studies were performed on potential pharmacodynamic interactions. The safety when combining aficamten with other negative inotropic drugs is discussed under clinical safety. No studies on genetic differences in PD response were performed.

PK-PD analyses and exposure-response analyses

PKPD analyses

The Applicant performed population pharmacokinetic-pharmacodynamic (PK-PD) and exposure response (ER) analyses of for LVEF and LVOT-G, based on core and site-read laboratory measurements collected in Studies CY 6021 and CY 6031. The selected exposure metric was the PopPK model (CYT-AFI-PMX-001) predicted average aficamten concentration 24 hr prior to the assessment (Cavg,24). PK-PD endpoints (log-transformed) were modelled as a direct linear response to aficamten exposure with baseline PD value as a covariate.

PKPD modeling revealed a consistent and reliable relationship between aficamten Cavg,24 and LVOT-G or LVEF in participants with oHCM in the Phase 2 and 3 studies (CY 6021 and CY 6031): core laboratory-read LVOT-G and LVEF were estimated to decrease by half with every 164 and 2,219 ng/mL increase in aficamten Cavg,24, respectively, indicating that increased aficamten exposure will decrease LVOT-G at a much greater rate than LVEF.

Although the slope of core laboratory-read LVEF as a function of aficamten Cavg,24 is only exactly linear in the log scale, it is approximately linear in the linear scale when Cavg,24 is < 500 ng/mL, a range of aficamten exposure that includes most of the observed Cavg,24 data from CY 6031. Within this aficamten exposure range, it can be expected that an approximately 2% decrease in LVEF would occur for every 100 ng/mL increase in aficamten Cavg,24.

Visual predictive checks for both readings indicate that the PKPD model sufficiently captures the central tendency and distribution of observed PD responses over the range of observed aficamten exposure, see Figure 7 and Figure 8.

Figure 7. Visual Predictive Check for Post-Valsalva LVOT-G

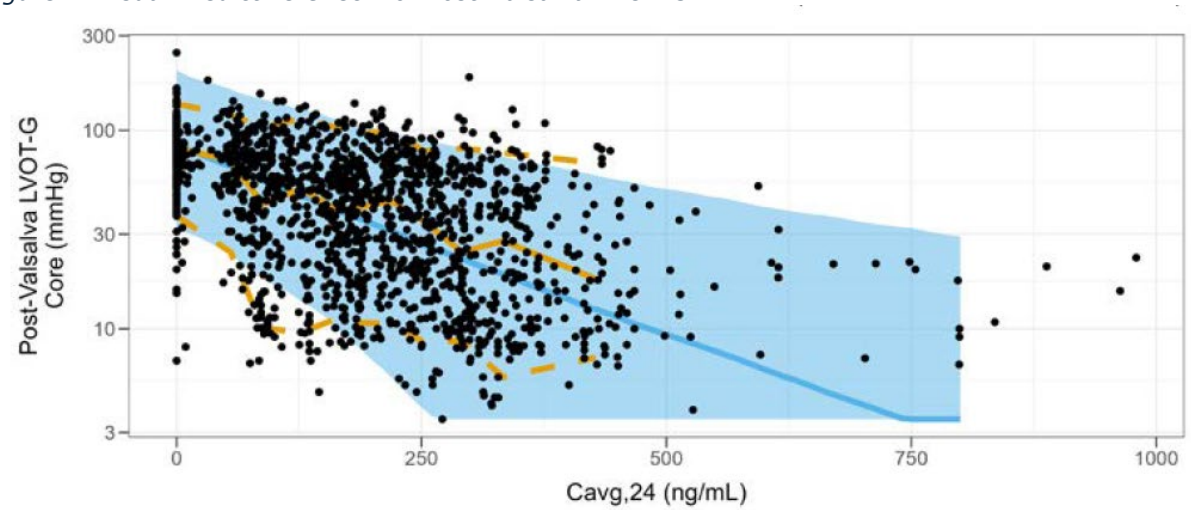
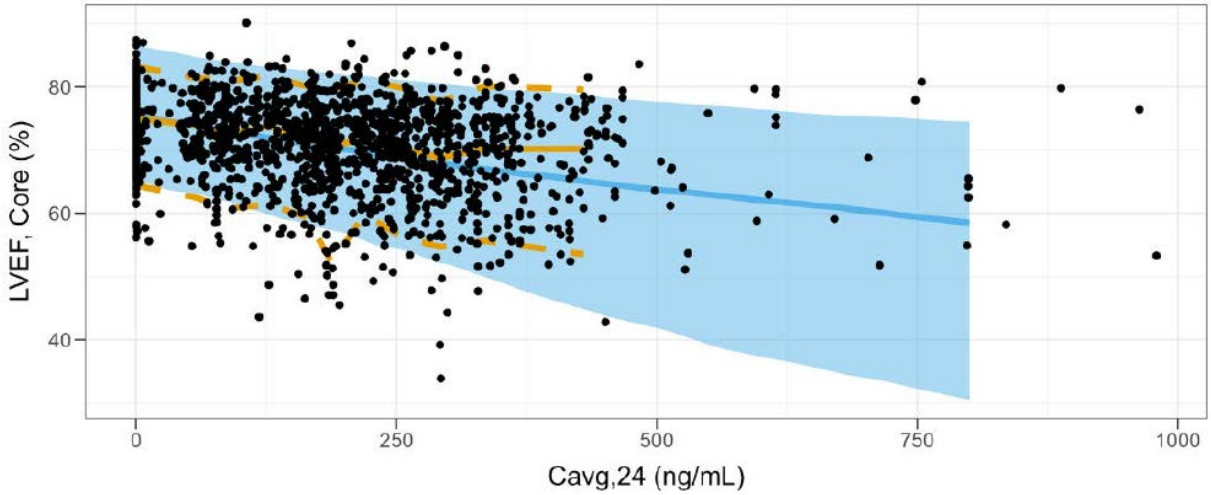


Figure 8. Visual Predictive Check for LVEF



Abbreviations: Cavg,24 = average concentration in 24 hours prior to measurement; LVOT-G = left ventricular outflow tract gradient. Note: The points are modeled Cavg,24 and measured LVOT-G values. The points are separated into one group with Cavg,24=0, and 10 other groups corresponding to deciles of positive Cavg,24. The gold lines are 5th, 50th and 95th percentiles of the points per decile, plotted at the median Cavg,24. Model predictions utilize concentration values evenly spaced between 0 and 800 ng/mL. Per concentration value, 1000 values are simulated using the LVOT-G PK-PD model, with samped baselines from CY 6021 and CY 6031. The blue shaded region represents the 5th to 95th percent prediction interval, and the solid blue line is the median.

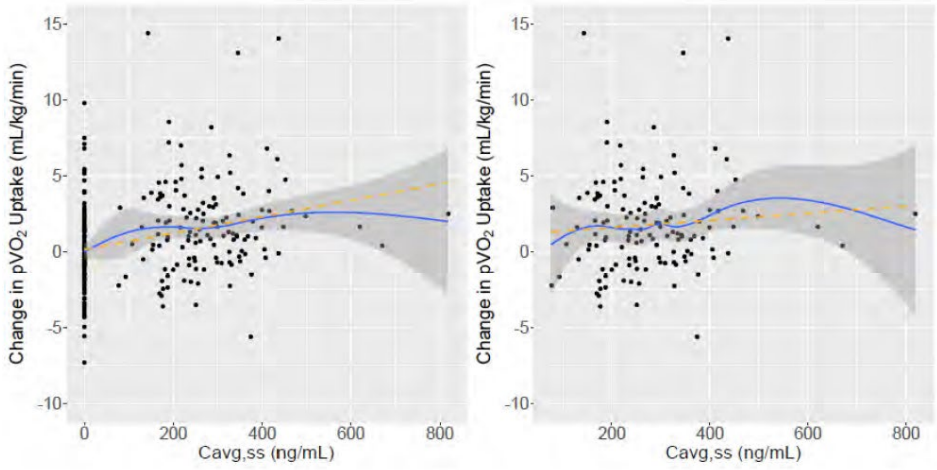
Exposure responses analyses for efficacy parameters

ER efficacy analysis for the primary endpoint, change in pVO2 by CPET from baseline to Week 24. Exploratory ER evaluations were conducted for the following secondary efficacy endpoints: change in KCCQ-CSS from baseline to Week 12 and Week 24, proportion of participants with ≥1 class improvement in NYHA functional classification from baseline to Week 12 and Week 24, change in hs-cardiac-TnI from baseline to Week 24, and change in NT-proBNP from baseline to Week 24.

Within the aficamten-treated group, change from baseline in pVO2 and ≥1 NYHA class improvement generally increased with increasing aficamten Cavg,ss, whereas change from baseline in NT-proBNP generally decreased with increasing aficamten Cavg,ss.

Figure 9 shows the relationship between change in pVO2 from baseline to Week 24 and aficamten Cavg,ss in all participants and in the aficamten-treated group alone. For the analysis set including all participants, there was a significant linear relationship indicative of an increased response in aficamten-treated participants compared to placebo. For participants in the aficamten-treated group, there was no significant relationship between aficamten exposures and change in pVO2 at Week 24. Similarly there was no relationship between Cavg,ss and change in KCCQ-CSS at Week 12 and Week 24 or with change in hs-cardiac-TnI at Week 24.

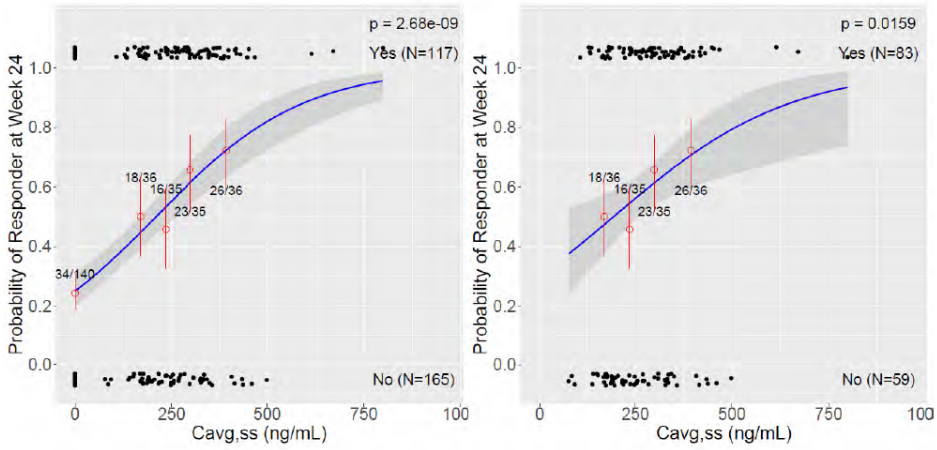
Figure 9. Relationship between Aficamten Cavg,ss and Change in pVO2 from Baseline to Week 24 for Placebo and Aficamten-Treated Participants (left panel) and Aficamten-Treated Participants Alone (right panel)



Abbreviations: Cavg,ss = model predicted average aficamten concentration at 24 hr prior to the assessment at Week 24; pVO_2 = peak oxygen uptake.
Notes: Orange dashed line is a linear regression. Blue line and gray shaded area are a locally estimated smoothing function and 95% confidence interval, respectively. Placebo participants shown at exposure = 0 in the left panel. P-value for slope <0.001 (left panel) and 0.3418 (right panel) (Table 7.8).

A linear logistic regression model described the relationship between Cavg,ss and the probablity of a being a responder (defined as a ≥1 NYHA Class improvement from baseline at Week 24), see Figure 10. For the analysis sets including all study participants (i.e., placebo and aficamten-treated participants), there was a significant ($p<0.001$) relationship between Cavg,ss and probability of being a responder at both Week 12 and Week 24, indicative of an increased response in aficamten-treated participants compared to placebo. Within the aficamten-treated group, there was a significant ($p<0.05$) relationship between aficamten Cavg,ss and probability of being a responder at Week 24.

Figure 10. Relationship between Aficamten Cavg,ss and Probability of Being a Responder (≥1 NYHA Class Improvement from Baseline to Week 24) for Placebo and Aficamten-Treated Participants (left panel) and Aficamten-Treated Participants Alone (right panel)

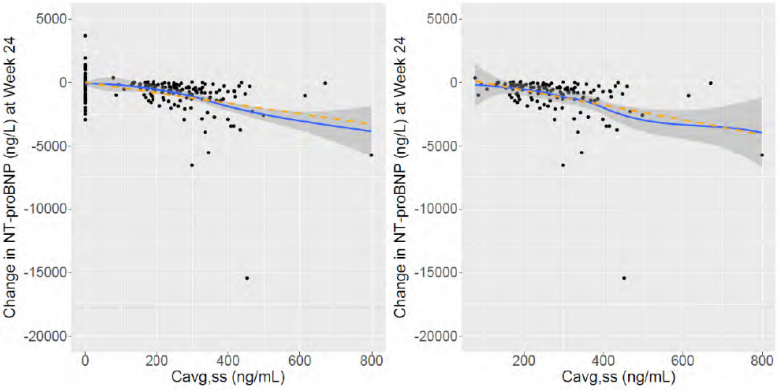


Abbreviations: Cavg,ss = model predicted average aficamten concentration at 24 hr prior to the assessment at Week 24; NYHA = New York Heart Association.

Notes: Yes and No refer to if participants were or were not responders (≥1 NYHA class improvement from Baseline). Participants were stratified into exposure quartiles. Red points are response rate and values are fraction of responders per exposure quartile plotted at the median exposure per quartile. Vertical red bars are 90% CIs of the response rate. Gray band represents the 5th to 95th percentile CI of a linear logistic regression fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test.

Figure 11 shows the relationship between aficamten Cavg,ss and change in NT-proBNP from baseline to Week 24 in all participants (including placebo and aficamten-treated participants) and in the aficamten-treated group alone. For both analysis sets, there was a significant ($p<0.001$) inverse linear relationship indicative of an increased response in aficamten-treated participants compared to placebo and a significantly ($p<0.001$) greater change from baseline in NT-proBNP at Week 24 with increasing aficamten exposure. Similar results were obtained for other exposures evaluated.

Figure 11. Relationship between Aficamten Cavg,ss and Change in NT-proBNP from Baseline to Week 24 for Placebo and Aficamten-Treated Participants (left panel) and Aficamten-Treated Participants Alone (right panel)



Abbreviations: Cavg,ss = model predicted average aficamten concentration at 24 hr prior to the assessment at Week 24; NT-proBNP = N-terminal pro B-type natriuretic peptide.

Notes: Orange dashed line is a linear regression. Blue line and gray shaded area are a locally estimated smoothing function and 95% confidence interval, respectively. Placebo participants shown at exposure = 0. P-value for slope is <0.001in both panels (Table 7.8).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Clinical pharmacology of aficamten has been investigated in 10 clinical studies and 33 in vitro studies evaluating permeability, metabolism, the interaction potential and protein binding. PopPK analyses, PBPK and exposure-response analyses were submitted to support the dose selection and dosing recommendations in special populations and with concomitant drug administration.

Aficamten has a single chiral centre and is manufactured by chiral specific intermediates. Chiral specific analysis showed that the product contains only the R-form. The R-form is more active than the S-form (Chuang et al., J. Med. Chem. 2021). Plasma samples from patients were analysed for the S-form, which was not detected. Hence interconversion does not occur.

Formulations

Two different formulations have been used in the clinical program: a granular formulation in capsules has been used in the SAD, MAD study and in all other studies the tablet formulation has been used. Comparable exposure of aficamten between the granule and tablet formulations has been demonstrated in study 6011.

The commercial tablets uses a % w/w blend whereas in earlier clinical studies a % w/w blend has been used. The % (w/w) formulation has been used in the pivotal phase 3 study and in 5 other phase 1 studies in healthy subjects. No comparative bioavailability study has been conducted between the % w/w and the % w/w blend tablets. No relevant difference in bioavailability is expected based on the dose proportional pharmacokinetics with the granules with % and % granule blends, comparable exposures between capsules and tablets, and the apparent high absorption of aficamten. The PopPK analysis with the phase 2 and phase 3 formulation included as covariate, indicated that the pharmacokinetics for the phase 3 (% w/w) and the phase 2 (% w/w) tablets is similar.

Four strengths, i.e., 5, 10, 15 and 20 mg are proposed for aficamten. All strengths are dose proportional in composition. In most studies the 5 mg strength has been used. In study 6012, the 20 mg tablets have been used to evaluate the food effect. No in vivo data are available for the 10 and 15 mg strengths. Adequate dissolutions tests have been provided. Hence, data obtained with the 5 mg and 20 mg strength can be extrapolated to the 10 and 15 mg strengths.

Absorption

In vivo absorption of aficamten is probably high. Excretion of radioactivity in urine and faeces in the form of (oxidised/reduced) metabolites is high with mean <6% of aficamten recovered in urine and faeces. Further support for high absorption comes from the slow excretion in urine and faeces with >70% of the radioactivity excreted after 48h. This is consistent with the permeability observed in Caco-2 cells (non-clin 0024). Solubility of aficamten was determined. Therefore, no effect of acid reducing agents is expected.

Absence of a food effect on the commercial tablet formulation (study 6012) supports the recommendation in the SmPC that aficamten can be taken with or without meals. This was also the recommendation in the phase 3 study.

Target population- Special populations

Aficamten exposures were approximately 25% higher in subjects with oHCM compared to healthy subjects. Data on the metabolite to parent ratio in patients with oHCM were comparable to those in

healthy subjects allowing extrapolation of the results from DDI studies conducted in healthy subjects to those in patients.

The applicant considered plasma aficamten Cmax at steady state of 142 - 470 ng/mL of the patients with oHCM population as the therapeutic window. However, most patients (115 out of 142) were uptitrated to 15 mg or 20 mg and had on average a 2-fold higher exposure than the lower limit of the proposed therapeutic window and the mean Cmax value in patients at the 15 and 20 mg was 305 ng/mL. Therefore a 1.5-fold increase is considered the upper limit and 2-fold decrease the lower limit. Since aficamten plasma concentrations at steady state have a low fluctuation, Cave and Ctrough values are considered to have the same 1.5-fold higher and 2-fold lower therapeutic window.

Impact of intrinsic factors is evaluated by popPK analysis (CYT AFI PMX 001). The popPK model appeared fit for this purpose. Body weight and sex were both found to be significant covariates on volume and clearance parameters of aficamten in PopPK analysis. Age, ethnic factors, and renal impairment were not significant covariates. No PK and safety data are available in subjects with severe renal impairment and with severe hepatic impairment. This has been acknowledged in the SmPC. Females had on average a 15% higher aficamten exposure compared to males with the same bodyweight. However, as females have on average a lower bodyweight, aficamten exposure was on average 30% higher in females compared to males. Body weight was a covariate in the popPK analysis. Aficamten plasma exposure is approximately 40% higher in subjects with the 5% lowest body weight compared to subjects with 95% highest body weight. Body mass index subgroups had no clinically relevant effect on efficacy in the pivotal study 6031. Considering the flat exposure-efficacy/safety relationship for aficamten in the range of doses evaluated and the proposed individualized aficamten dose titration strategy, no dose adjustment of aficamten is warranted based on sex or body weight. However, a multivariate analysis from pivotal study CY6031 showed that only LVOT-G was a statistically significant covariate with an odds ratio value and the 95% CI greater than one. Additionally, scatter plot analyses of study CY 6031 showed that all participants with baseline Valsalva LVOT-G $\geqslant$ 100 mmHg were titrated to $\geqslant$10 mg. Based on the analysis, the Applicant is proposing to include in the SmPC 4.2 section the following recommendation "A starting dose of 10 mg should be considered for patients with peak LVOT-G $\geqslant$ 100 mmHg" which is endorsed.

Moderate hepatic impairment (Child-Pugh B, study 6017) had no impact on the exposure of aficamten.

Metabolism - interactions

In vitro phenotyping studies with microsomes and hepatocytes indicated that aficamten is slowly metabolised but multiple CYP enzymes could be involved in the slow formation of metabolites M1a and M1b. In vivo, M1a and M1b were formed quite readily, with a tmax 4-6 hours after administration. Four hours after administration M1a and M1b accounted for more than 50% of aficamten related material in plasma, with aficamten contributed 25%-30%. Thus, during the absorption and distribution phase, aficamten is extensively metabolised.

In contrast, plasma elimination of aficamten was slow with an elimination half-life of approximately 80h. This half-life was prolonged by co-administration of fluconazole (inhibitor of CYP2C9, CYP2D6 and CYP3A4), and shortened by carbamazepine a moderate to strong inducer of CYP3A4, CYP2C9, and CYP2C19 indicating that the long elimination plasma half-life is metabolism mediated. The metabolites M1a and M1b have the same half-life as aficamten which suggest that the elimination of M1a and M1b is formation rate limited.

A substantial number of interaction studies with itraconazole (strong CYP3A4 inhibitor), carbamazepine (moderate-strong inducer of CYP3A4 and CYP2C enzymes), paroxetine (strong CYP2D6 inhibitor), fluoxetine (strong CYP2D6 and CYP2C19 inhibitor) and fluconazole (strong CYP2C19, moderate CYP2C9 and CYP3A4 inhibitor) evaluated the in vivo interaction potential for aficamten as object. Itraconazole,

paroxetine and fluoxetine increase aficamten exposure < 1.5-fold. However, there are some unexpected results in these *in vivo* DDI studies, i.e., the increase in Cmax in aficamten in the interaction studies with paroxetine and fluoxetine is unlikely due to CYP enzyme inhibition. However, it is uncertain if the mechanism that leads to increase in Cmax also may affect the AUC to some extent and therefore overestimates the effect of CYP2D6 and CYP2C19 inhibition by paroxetine and fluoxetine. The M1a/M1b metabolite:parent ratio was changed by paroxetine and fluoxetine indicating that the metabolism of aficamten was inhibited by these two inhibitors. On the other hand, the M1a/M1b metabolite:parent ratio by itraconazole suggested that the main metabolism pathways were not affected by itraconazole. This might be explained by potential inhibition of the elimination of the metabolites by itraconazole. Overall, no adjustment is needed when aficamten is co-administered with either a strong CYP3A4, or strong CYP2D6 or strong CYP2C19 inhibitor.

On the other hand, fluconazole, a multi-enzyme inhibitor (moderate CYP2C9, moderate CYP3A4, strong CYP2C19 inhibitor), increased aficamten exposure 3.8-fold. A contraindication is proposed for fluconazole. Therefore, there is a potential safety concern for other co-medications that inhibit multiple enzymes including CYP2C9.

Polymorphism of CYP2C9 has not been investigated in the clinical studies but the prevalence of polymorphisms of CYP2C9 is low and polymorphisms do not lead to complete loss of function. The effects of CYP inhibitors on aficamten exposure in poor metabolisers have been predicted by co-medications by PBPK modelling (Table 12). Since aficamten is titrated based on effect and the effect of single inhibitors on aficamten exposures in poor metabolisers were modest, geno- or phenotyping for CYP2C9 polymorphisms is considered not necessary.

PBPK modelling but also an algebraic method were used to estimate the effects of other CYP2C9 inhibitors on aficamten exposure. The application of the PBPK model is considered high impact since it aims to provide dosing recommendations of other inhibitors/inducers not tested in vivo. The PBPK model is a top-down model and there are several in vivo interaction studies that were conducted with itraconazole, paroxetine, fluoxetine, fluconazole and the inducer carbamazepine, and therefore the risk of the model to predict >1.5-2 fold difference with true values for these enzymes is considered low.

Significant increases in aficamten exposure have been observed by concomitant treatment with fluconazole, resulting in a proposed contraindication. To provide proper dosing recommendations for other drugs that are an inhibitor of CYP2C9 and other enzymes, it is essential to elucidate which enzymes and to what extent are involved in the elimination of aficamten. To estimate the contribution of the various CYP enzymes to the elimination of aficamten, the in vivo DDI study results with a strong inhibitor were used in PBPK modelling but also an algebraic method. This is a well-established method. Instead of strong inhibitors, for polymorphic enzymes polymorphism that leads to an unfunctional enzyme can be used (ICH-M12). However, polymorphisms of CYP2C9 do not lead to complete loss of function, on average a third of CYP2C9 activity is remaining. Because there is currently no strong inhibitor of the major enzyme CYP2C9, that can be administered to healthy subjects, the contribution of CYP2C9 to metabolism of aficamten is deduced by subtraction of the contributions of other enzymes CYP3A4, CYP2D6 and CYP2C19 based on the in vivo DDI studies with strong inhibitors for these enzymes. Thus, although the approach is understood, this is prone to higher uncertainties in the estimation of fm of CYP2C9. This uncertainty is similar for the algebraic method as for the PBPK modelling because both use the fm fractions based on the observed in vivo DDI studies with strong inhibitors and both underestimate the interaction by fluconazole by 1.5-fold.

Therefore, it is unknown whether the predicted interactions by other inhibitors not used in the in vivo DDI studies are also underestimated. As a consequence, the required recommendations in the SmPC for co-medications that are multi-enzyme inhibitors or strong CYP2C9 inhibitors, are uncertain. An additional DDI study with a CYP2C9 multi-enzyme inhibitor e.g. with fluvoxamine could address this

uncertainty. Also additional sensitivity analyses could provide a more complete picture of the potential impact of these inhibitors on the exposure of aficamten.

Additional sensitivity analyses have been provided to get a more complete picture of the potential impact of these inhibitors on the exposure of aficamten. These sensitivity analyses encompassed an increase in CYP2C9 fm with a corresponding decrease in CYP2D6 fm (0.21 → 0.01) or CYP3A fm (0.21 → 0.01), a decrease in CYP2D6 involvement (fm 0.21 → 0.01) with an increase in CYP2C19 involvement (fm 0.03 - → 0.24) was applied, and a higher affinity of fluconazole for CYP2C9 (decrease in Ki value).

Sensitivity analyses increasing CYP2C9 fm at the expense of CYP3A fm, decreased both fluconazole and itraconazole DDI prediction accuracy and is an unlikely scenario. Increasing CYP2C9 fm at the expense of CYP2D6 fm increases predicted aficamten AUC ratio (AUCR) after fluconazole coadministration, but only at the expense of the prediction accuracy for paroxetine and fluoxetine. Considering this scenario for the inhibitors not studied in vivo: the predicted effect of the strong CYP2C9 inhibitor sulfaphenazole increased form 2-fold to 3-fold increase whereas the effects of the multi-enzyme inhibitors fluvoxamine and voriconazole did not change much and are predicted to increase aficamten exposure by 2-fold. Therefore, the additional sensitivity analyses did not indicate an extra risk for multiple enzyme inhibitors, but there is some more uncertainty for strong CYP2C9 inhibitors. Currently we have no medicinal products that are strong CYP2C9 inhibitors approved in the EU. Another sensitivity analysis assuming that aficamten is not metabolized by CYP2D6 and allocating the fm of CYP2D6 to CYP2C19 resulted in a better prediction of the fluconazole observed effect, but this also resulted in an increased predicted effect of voriconazole 2.6-fold in CYP2C9 normal metabolisers and 3.9-fold in CYP2C9 poor metabolisers and thus would impact the dosing recommendations. This scenario is considered not likely because paroxetine (CYP2D6 inhibitor) and fluoxetine (CYP2D6 and CYP2C19 inhibitor) had very similar effects on aficamten pharmacokinetics, which supports the involvement of CYP2D6. The sensitivity analysis regarding the affinity (Ki value) of fluconazole, indicated that the predicted effect of fluconazole on aficamten is very sensitive for the Ki value of fluconazole for CYP2C9. Change in Ki did not affect the predictions with the other studied and not studied inhibitors. In that respect, an increased affinity of fluconazole for CYP2C9 could explain underprediction of fluconazole's effect on aficamten without influencing (negatively) the predictions for the other inhibitors, it is, however, agreed with the applicant that the default Ki value for fluconazole should be used because a) the inhibitor file of fluconazole does not indicate any consistent underprediction with other CYP2C9 substrates and b) the applicant showed that use of a Ki value that predicts aficamten interaction accurately, will overestimate the DDI of other CYP2C9 substrates. It is not known why the PBPK modelling did not predict the interaction very well but the sensitivity analyses indicated a rather constant effect on aficamten exposures by inhibitors not studied in vivo.

In the clinical phase 2 & 3 studies 12 patients had amiodarone co-administered. Amiodarone is a mild to moderate CYP2C9 inhibitor and weak inhibitor of CYP2D6 and CYP3A4, hence a multi-enzyme inhibitor. Aficamten exposures in these subjects were at each dose level within the exposure ranges of the other patients. This is reassuring. Including amiodarone in the PBPK analysis would be helpful selecting which scenario is most likely and subsequently inform on the dosing strategy for other CYP2C9 (multi-enzymes) inhibitors. It is, though, acknowledged that only a research substance file is available.

The agreed proposal is to contraindicate concomitant use with once daily dosing fluconazole and rifampicin. No dose reduction of aficamten is considered needed when treated with a single dose / once weekly dosing of fluconazole. Other medicinal products with expected similar effects on aficamten exposures e.g. adagasib and St John's Wort, respectively, were included in Section 4.3 of the SmPC of aficamten (contra-indications). Further, it is recommended to avoid concomitant use of CYP2C9 strong inhibitors, and dosing instructions are proposed for drugs that are inhibitors for multiple enzymes including CYP2C9. Since all predictions thus far with CYP2C9 (multi-enzyme) inhibitors resulted in >

1.5-fold increase in aficamten exposure, the maximal aficamten dose is 15 mg when CYP2C9 (multi-enzyme) inhibitors are co-administered. In addition, a longer dose titration schedule than 2 weeks should be considered when interacting medications are initiated whilst on stable aficamten treatment, depending on the half-life of aficamten in presence of the inhibitor and/or on the half-life of the inhibitor, whichever is the longest.

Aficamten, M1a and M1b exhibit low interaction profile to act as *precipitant* for CYP enzymes: no inhibition occurred at relevant concentrations, induction of CYP1A2 cannot be fully excluded because all three compounds showed some induction potential. The in vivo induction potential of aficamten and metabolites for CYP1A2 seems low based on the slope method. No in vivo DDI study is considered necessary.

Aficamten was not a substrate for Pgp, BCRP and the uptake transporters OATP1B1 and OATP1B3. Since aficamten is not excreted in the urine, evaluation of the renal transporters is not necessary.

For all transporters except Pgp, the estimated IC50 values of aficamten, M1a and M1b were above the threshold values of for potential risk. The potential for clinically relevant inhibition of P-gp by aficamten could not be excluded. Consequently, a clinical DDI study was conducted to evaluate the effect of aficamten on the PK of P-gp substrates (6014). Considering the ~25% increase in the plasma dabigatran Cmax and AUC∞, aficamten is considered a weak inhibitor of Pgp and may be co-administered with P-gp substrates without dose adjustment.

Pharmacodynamics

Aficamten inhibits cardiac myosin, reducing the cardiac contractile force and alleviating obstruction of the left ventricular outflow tract (LVOT). LVOT obstruction is a primary cause of exercise intolerance, symptoms, and morbidity in the majority of patients with symptomatic oHCM. Reduction of LVOT obstruction decreases intraventricular systolic pressure and may potentially, although this has not been studied, also prevent progression of hypertrophy and fibrosis. Support for the mechanism of action comes from the PD effects on LVOT-G and LVEF, as well as other echocardiographic parameters.

CY 6011 was the first-in human trial of aficamten, investigating the safety and tolerability of single and multiple ascending doses of aficamten orally administered to healthy adults. Results from the single ascending doses part demonstrated that doses of 40 and 50mg were pharmacologically active, as demonstrated by decreases in LVEF. The highest dose of 75mg led to a reduction of LVEF > 15% in the first subject, which precluded further dose escalation. In the multiple ascending dose part, the incidence of at least 5% reductions in LVEF occurred after multiple doses of 10 mg aficamten, which was also the highest multiple dose administered in the study. Thus, the single dose of 50 mg and the multiple dose of 10 mg were identified to be pharmacologically active doses. Both these doses were also generally well tolerated by the healthy adult subjects in this study. The results of this study were used to further guide dose selection for the phase 2 and 3 trials, which is described in detail in the dose finding part of the clinical efficacy.

Secondary pharmacology was focussed on the QTc effects of aficamten. A phase 1 single-center, randomized, double-blind, positive- and placebo-controlled, single-dose, 3-way crossover thorough QT study (CY 6019) was conducted to assess the impact of a single dose of 50 mg aficamten on QT/QTc interval in 34 healthy participants. Various concentration QT models were fit on the data (with different combinations of the 3 analytes (aficamten, metabolite CK-3834282, and metabolite CK-3834283)). All 5 models were comparable in terms of model fit and the predicted ddQTcF values were also comparable across all tested models. This study demonstrated that a single dose of 50 mg did not increase the QT interval. PK results demonstrated that a 50 mg dose in healthy adults led to similar concentrations as those observed at the intermediate dose of 15 mg daily in patients. Although the 15

mg dose may produce lower concentrations compared to the highest dose of 20 mg used in oHCM, the overall data strongly suggest no evidence of a potential for QTc elongation. This is in agreement with the non-clinical studies where the half-maximal inhibitory concentration (IC50) values for the inhibitory effect of aficamten on the hERG potassium current was estimated to be > 10 µM, which far exceed the maximal clinical Cmax values at the maximum recommended dose of 20 mg daily dose in patients with oHCM. Further, in the safety pharmacology study (nonclin-0013), there were no drug-related effects on quantitative or qualitative electrocardiogram (ECG) parameters at any dose level evaluated in telemetered dogs dosed with aficamten for 7 consecutive days.

No studies on genetic differences in PD response were performed.

No dedicated studies were performed on potential pharmacodynamic interactions. The safety when combining aficamten with other negative inotropic drugs is discussed under clinical safety.

PK-PD models were developed to link exposure (Cavg,24) to LVEF and LVOT-G for both core and site-read laboratory measurements for 183 aficamten-treated participants from study CY 6021 (dose-finding Phase 2 study) and study CY 6031 (pivotal Phase 3 study). The model did capture the central tendency, although a slight overprediction of variability is observed. LVOT-G and LVEF were estimated to decrease by half with every 164 and 2,219 ng/mL increase in aficamten concentration, respectively, which indicates that increased aficamten exposure will decrease LVOT-G at a much greater rate than LVEF. This further supports the use of dosing strategy based on both LVOT-G targets and LVEF safety thresholds.

Exposure response analyses were performed for other efficacy parameters, which demonstrated a significant exposure response relationship ($p<0.05$) for probability of $\geq$1 NYHA class improvement and NT-proBNP change from baseline to Week 24, both with or without placebo. For change in pVO2 max, KCCQ-CSS and hs-cardiac troponin I, no significant exposure response relationship was found in the aficamten-treated group, most likely due to the fact that dose selection was titrated based on achieving LVOT-G targets and maintaining normal LVEF. Potential confounding or a less direct relationship with endpoints may also play a role in the lack of relationships. Since dosing is already optimized using a PD marker, the absence of an exposure-response relationship for the efficacy endpoints is not a concern and does not indicate a problem with the efficacy of aficamten.

Dose justification is described under section Clinical Efficacy, to prevent duplication of data. Reference is made to the Discussion on clinical efficacy section for details on the adequacy of the dosing strategy.

2.6.4. Conclusions on clinical pharmacology

In general, the pharmacokinetics of aficamten and its inactive major metabolites M1a and M1b have been sufficiently investigated in healthy subjects and subjects with oHCM. The major uncertainty in the pharmacokinetics of aficamten is that it is not clear to what extent which enzymes are involved in its metabolism. Significant increases in aficamten exposure have been observed by concomitant treatment with fluconazole, resulting in a proposed contraindication. To provide proper dosing recommendations for other drugs that are an inhibitor of CYP2C9 and other enzymes, it is essential to elucidate which enzymes to what extent are involved. A series of sensitivity analyses resulted in recommendations to avoid concomitant use of CYP2C9 strong inhibitors, and dosing instructions are proposed for drugs that are inhibitors for multiple enzymes including CYP2C9. Dosing recommendations and contraindications have been provided when aficamten is used concomitantly with (multi-enzyme) inhibitors of CYP2C9 and strong inducers of PXR in the SmPC sections 4.2, 4.3 and 4.5, include respective recommendations for concomitant use and dose adjustments and were considered acceptable.

The pharmacodynamic part of the submitted dossier included the first-in-human trial in healthy adults that helped determine a safe and pharmacodynamically effective starting dose to further guide dose selection, a thorough QTc study which excluded an effect of aficamten on QTc prolongation, PK-PD modelling on the inverse logarithmic relationship of aficamten concentration and both LVOT-G and LVEF, and exposure-response analyses which demonstrated a lack of exposure response relationships for most efficacy parameters. Generally, the pharmacodynamics of aficamten have been sufficiently evaluated.

2.6.5. Clinical efficacy

The efficacy of aficamten for the treatment of symptomatic oHCM in adults is based on data from the pivotal Phase 3 Study CY 6031 and supported by results from the Phase 2 Study CY 6021 and the open-label extension Study CY 6022.

Table 11. Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
SEQUOIA-HCM (CY-6031)	Feb 2022 to Dec 2023 Completed 282 participants (142 aficamten, 140 placebo)	A Phase 3, Multi-center, Randomized, Double-blind, Placebo controlled	Site-read echocardiography guided dose optimization scheme: Aficamten 5, 10, 15, or 20 mg QD or placebo for up to 24 weeks	Male and female adult participants with symptomatic oHCM receiving stable doses of background therapy individually optimized per local practice
REDWOOD-HCM (CY-6021)	Jan 2020 to Feb 2023 Completed Cohort 1: 22 participants Cohort 2: 20 participants Cohort 3: 13 participants Cohort 4: 41 participants	A Multi-center, Randomized, Double-blind, Placebo-controlled, Dose-finding Study	Site-read echo-cardiography guided dose optimization scheme: Cohort 1: Aficamten 5, 10, and 15 mg QD or placebo for up to 10 weeks Cohort 2: Aficamten 10, 20, and 30 mg QD or placebo for up to 10 weeks Cohorts 3 and 4: All participants assigned aficamten 5, 10, and 15 mg QD for up to 10 weeks	Male and female adult participants with symptomatic HCM Cohorts 1-3: Participants with oHCM receiving stable doses of background therapy Cohort 4: Participants with nHCM receiving stable doses of background therapy
FOREST-HCM (CY-6022)	May 2021 to 31 Oct 2023 (data cutoff) Ongoing	Open-label extension study in participants with oHCM or nHCM (CY 6022 [FOREST-HCM]) who are continuing from other	Site-read echocardiographyguided dosing (dose optimization allowed throughout the study): All participants	Male and female adult participants with symptomatic HCM who completed a previous study of aficamten (CY 6021 or

	Enrolment at data cutoff: 213 participants with oHCM, 34 participants with nHCM	studies, including CY 6021 and CY 6031.	assigned aficamten 5, 10, 15, or 20 mg QD for up to 5 years	CY 6031)

2.6.5.1. Dose response study(ies)

Dose selection for the Phase 3 study CY 6031

The first-in-human study (CY 6011) established the doses (up to 50 mg as a single oral dose or up to 10 mg following multiple doses; higher than 10 was not tested in CY 6011) at which aficamten was both physiologically effective at reducing LVEF (5-15%) and well tolerated in healthy participants. Briefly, single doses of aficamten 40 and 50 mg, and multiple daily doses of aficamten 10 mg administered for 14 days to healthy participants were determined to be pharmacologically active, with several participants experiencing mean change from baseline in LVEF values approaching 5% at 1.5 hours postdose. The effect of aficamten on LVEF reversed within 24 to 48 hours of dose discontinuation. Participants who had decreases in LVEF to < 50% remained asymptomatic. In the single ascending dose part, a relationship between plasma concentration and LVEF change was statistically significant, in the multiple ascending dose part, no such relationship could be demonstrated.

Based on these results, the clinical development program sought to maintain pharmacodynamically active aficamten plasma concentrations, but with the understanding that supratherapeutic concentrations may result in systolic dysfunction (exaggerated PD effect), leading to decreases in stroke volume and cardiac output, compensatory increases in heart rate, and potentially clinical heart failure. Based on that premise, a conservative phase 2 dose selection strategy was employed where participants with oHCM received aficamten 5 mg (Cohorts 1 and 3) or 10 mg (Cohort 2) as the starting doses since they were deemed well-tolerated in healthy participants in CY 6011. Dose escalation, in increments of 5 mg, up to 15 mg (Cohorts 1 and 3) or, in increments of 10 mg, up to 30 mg (Cohort 2) only occurred when the participant's current dose was well-tolerated and the participants met predefined echocardiography-based escalation criteria. The designs of the phase 2 dose finding study was as follows. The study consisted of 4 cohorts. For Cohorts 1 and 2, participants with oHCM and not receiving disopyramide were randomized 2:1 to active or placebo treatment and received up to 3 escalating doses of aficamten based on echocardiographic guidance (5, 10, and 15 mg in Cohort 1 and 10, 20, and 30 mg in Cohort 2) or placebo. Cohort 3 consisted of participants with oHCM whose background HCM therapy included disopyramide. All participants in Cohort 3 received up to 3 escalating doses of aficamten (5, 10, and 15 mg) based on echocardiographic guidance. Cohort 4 consisted of participants with non-obstructive HCM (nHCM) whose background therapy included beta-blockers and/or calcium channel blockers, either as monotherapy or combined. Participants receiving disopyramide were excluded from Cohort 4. Cohort 4 participants received up to 3 doses of aficamten (5, 10, and 15 mg), titrated based on echocardiographic guidance. In all 4 cohorts, treatment duration was 10 weeks with a 4-week follow-up period after the last dose. Participants received dose 1 for 2 weeks. At Week 2, participants could be up-titrated to dose 2 if either of the following conditions was met on echocardiography, otherwise, the participant remained on dose 1:

1) Resting LVOT-G ≥ 30 mmHg and the biplane LVEF ≥ 50% OR 2) Resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G ≥ 50 mmHg, and the biplane LVEF ≥ 50%. After 2 more weeks on the assigned dose, participants were again assessed for dose titration based on echocardiography. Participants were up-

titrated to the next higher dose if either of the above conditions was met. Otherwise, the participant remained on the same dose, or if LVEF was < 50% at week 4, the participant was returned to a prior dose level or to placebo if the participant was on Dose 1.

In cohort 1 of study CY 6021 (N = 14 participants in the aficamten arm), the dose titration scheme employed doses of 5, 10, and 15 mg of aficamten. The 5 mg starting dose was pharmacodynamically effective and well-tolerated by all participants; 4 participants did not require further dose escalation for the rest of the study as their resting LVOT-G was < 30 mmHg and Valsalva LVOT-G was < 50 mmHg. The 10 mg dose was pharmacodynamically effective and well-tolerated in the rest of the participants; 5 additional participants did not require further dose escalation as they had achieved their treatment targets. Finally, there were 5 participants who achieved the highest dose of 15 mg, which was well-tolerated and pharmacodynamically effective. At the end of treatment visit at 10 weeks, 3 participants on the 15 mg dose still had a Valsalva LVOT-G > 50 mmHg, suggesting a higher dose may have been useful in some participants.

Therefore, in Cohort 2 of Study CY 6021 (N = 14 participants in active arm), higher doses of 10, 20, and 30 mg of aficamten were evaluated to further explore the dose- and concentration response. The 10 mg starting dose was pharmacodynamically effective and well-tolerated by all participants; 8 participants (Table 14) did not require further escalation for the rest of the study as their resting LVOT-G was < 30 mmHg and Valsalva LVOT-G was < 50 mmHg. Therefore, 6 participants were escalated to the 20 mg dose; 4 participants achieved target gradients at this dose level (although 1 participant was down-titrated to 10 mg due to LVEF < 50%), while 2 participants were escalated further to 30 mg. One of the 2 participants on the 30 mg dose was down-titrated to 20 mg due to LVEF < 50%, and the other participants did not achieve an adequate PD response. These data suggested that the 30 mg dose is not likely to add substantial clinical benefit versus risk; therefore, 20 mg was selected as the highest dose in the Phase 3 trial. The 25 mg dose was not evaluated.

Table 12. Highest Doses Achieved in Study CY 6021, Cohort 1 and Cohort 2

	Highest Dose Achieved (n)					
	Placebo	5 mg	10 mg	15 mg	20 mg	30 mg
Cohort 1 (n = 21)	7	4	5	5	-	-
Site-read LVEF < 50%	0	0	0	0	-	-
Cohort 2 (n = 20)	6	-	8	-	4[a]	2[a]
Site-read LVEF < 50%	0	-	0	-	1	1
Cohort 1 and 2 (n = 41)	13	4	13	5	4[a]	2[a]
Site-read LVEF < 50%	0	0	0	0	1	1

LVEF = left ventricular ejection fraction.
[a] One participant down-titrated to lower dose based on site-read echocardiography.

Rationale for the phase 3 dosing strategy

A consistent feature of the Phase 2 and 3 programs was the use of an individualized echocardiography-guided dose titration strategy to maximize achievement of target LVOT-G and maintain normal LVEF. For participants with oHCM in the phase 2 dose finding study (CY 6021), 3 opportunities for dose titration were provided (weeks 2, 4, and 6). The phase 3 trial (CY 6031) followed a similar dose titration strategy as implemented in Study CY 6021; however, the LVOT-G target criteria for dose titration was simplified by focusing on the Valsalva LVOT-G only. The Valsalva LVOT-G target was reduced from 50 mmHg to 30 mmHg to maximize the potential therapeutic benefit of aficamten.

Importantly, in contrast to Study CY 6021, the lower limit of LVEF for dose escalation in CY 6031 was increased from 50% to 55% to provide a safety margin from the threshold of LVEF (< 50%) that triggered dose reduction in both studies. If LVEF was < 50% at any time, the participant was returned to the prior dose level, or to placebo if the participant was on 5 mg. In CY 6031, participants were able to receive up to 4 increasing dose levels (5, 10, 15, and 20 mg) of aficamten over 3 dose titration opportunities. Doses of aficamten were individually titrated at Weeks 2, 4, and 6 using echocardiography. Dose escalation occurred only if a participant had a Valsalva LVOT-G ≥ 30 mmHg and an LVEF ≥ 55%. Echocardiograms at Weeks 8 and 12 were also performed, and the dose was down-titrated if the LVEF was < 50%. If LVEF was < 50% at any time, the participant was returned to the prior dose level, or placed on placebo if the participant was on 5 mg.

Evaluation of Selected Doses in CY 6031

CY 6031 is described in detail under main studies below, and the doses evaluated are described here in short. Patients started on 5 mg and were up titrated to higher doses until Valsalva LVOT < 30 mmHg, provided LVEF ≥ 55%. All dose adjustments were guided by site-read echocardiographic findings, and there was no use of aficamten plasma concentration levels to guide dosing. An overview of the dose titration is shown in Table 15.

Table 13. Dose modifications in CY 6031

Action	Valsalva LVOT-G	Biplane LVEF
Reduce Dose[a]	Any	< 50%
No Dose Change	Any	50% to < 55%
	< 30 mmHg	≥ 55%
Increase Dose	≥ 30 mmHg	≥ 55%

LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient.

[a] Once a participant's dose is down-titrated, no further escalation is permitted. If LVEF < 50% on 5 mg, the participant will receive placebo.

Of the 142 participants treated with aficamten, 68 (48.6%) achieved an aficamten dose of 20 mg daily at week 8; of these participants, 3 were subsequently down-titrated to 15 mg daily, and no participant had a further dose reduction. A total of 49 participants (35.0%) achieved an aficamten dose of 15 mg daily at Week 8, and 3 were subsequently down-titrated to 10 mg daily, with no further dose reductions. The week 8 aficamten dose was 10 mg daily for 18 participants (12.9%) and 5 mg daily for 5 participants (3.6%); no dose reductions occurred for participants at either of these dose levels. Two participants discontinued treatment prior to Week 8 (due to participant withdrawal from the study); 1 participant had been titrated to 15 mg daily prior to discontinuation of treatment, and 1 participant had been titrated to 10 mg daily prior to discontinuation of treatment.

Table 14. Summary of Aficamten Dose Achieved by Visit in CY 6031 (Safety Analysis Set)

Visit	Aficamten Dose Achieved					
	0 mg n (%)	5 mg n (%)	10 mg n (%)	15 mg n (%)	20 mg n (%)	Overall n (%)
Day 1	0	142 (100)	—	—	—	142
Week 2	0	21 (14.8)	121 (85.2)	—	—	142
Week 4	0	8 (5.7)	35 (24.8)	98 (69.5)	—	141
Week 6	0	5 (3.6)	17 (12.1)	50 (35.7)	68 (48.6)	140
Week 8	0	5 (3.6)	18 (12.9)	49 (35.0)	68 (48.6)	140
Week 12	0	5 (3.6)	19 (13.7)	48 (34.5)	67 (48.2)	139
Week 16	0	5 (3.6)	21 (15.2)	48 (34.8)	64 (46.4)	138
Week 20	0	5 (3.6)	21 (15.3)	48 (35.0)	63 (46.0)	137
Week 24	0	5 (3.6)	21 (15.3)	48 (35.0)	63 (46.0)	137

As shown in Table 16, the majority of participants were titrated to the 2 highest doses. The proportion of participants who achieved doses of 5 mg, 10 mg, 15 mg, and 20 mg were 3.6%, 12.9%, 35.0% and 48.6% at week 8 (the end of the titration phase) and 3.6%, 15.3%, 35.0%, and 46.0% at week 24, respectively.

Commercial dosing strategy

The goal of the proposed commercial aficamten daily dose regimen is to maintain the favorable benefit-risk profile established in the Phase 3 trial (CY 6031), while allowing for more flexible clinic visit schedules for patients with oHCM. To do this, only minor changes were needed to translate the echocardiography-based dose titration criteria and frequency from that studied in phase 3 to the proposed commercial administration of aficamten to patients with oHCM. The Applicant proposes to use the same dosing criteria for uptitrating, maintaining or reducing doses as used in CY 6031, but proposes to increase the window of echocardiography from 2 weeks to 2-8 weeks. The phase 3 trial (CY 6031) used a defined schedule for aficamten dose titration: weeks 2, 4, and 6, with the opportunity to down-titrate if needed at Weeks 8 and 12. Week 8 represented the start of a predefined maintenance phase during which participants with oHCM received echocardiographic assessments every 4 weeks through the end of study at Week 24. A titration and maintenance clinic visit frequency of every 2 and 4 weeks, respectively, would place an unnecessary burden on patients with oHCM and the healthcare system. Therefore, a simpler practical dose selection strategy that allows for the option of a more flexible schedule for dose titration visits of 2 to 8 weeks for echocardiographic assessments is proposed based on additional clinical trial simulations.

The proposed instructions are shown in Table 17.

Table 15. Tabulated Proposed Aficamten Echocardiography-based Dose Titration Criteria with Instructions for Dose Titration, Timing of Next Potential Dose Titration, and Management of Potential Events of LVEF < 50%

Row	Current			Dose Titration	Next	
	LVEF (%)	LVOT-G (mmHg)	Dose (mg)		Phase	Visit
1	≥ 55	≥ 30	5 to 15	Increase by 5 mg	Titration	2 to 8 weeks
2	≥ 55	≥ 30	20	No change	Maintenance	Approximately 6 months
3	≥ 55	< 30	Any			
4	≥ 50 to < 55	Any	Any	No change	Maintenance	Approximately 3 months
5	≥ 40 to < 50	Any	10 to 20	Decrease by 5 mg	Titration	2 to 8 weeks
6	≥ 40 to < 50	Any	5	Interrupt for ≥ 7 days; Resume at 5 mg when LVEF ≥ 55%[a]		
7	< 40		5 to 15			
8	< 40	Any	20	Interrupt for ≥ 7 days; Resume at 10 mg when LVEF ≥ 55%[a]		

LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient.
[a] Dependent on intercurrent illness and patient clinical status.

To justify the larger window of echocardiography, the Applicant performed simulations which explores dose titration intervals of 2, 4, 6 or 8 weeks, and does not have a fixed time to enter maintenance. Rather, participants enter maintenance when LVEF and post-Valsalva LVOT-G endpoints enter an acceptable range; conversely participants go back into titration if endpoints fall out of range. The results are shown in Figure 12, Table 18 and Table 19.

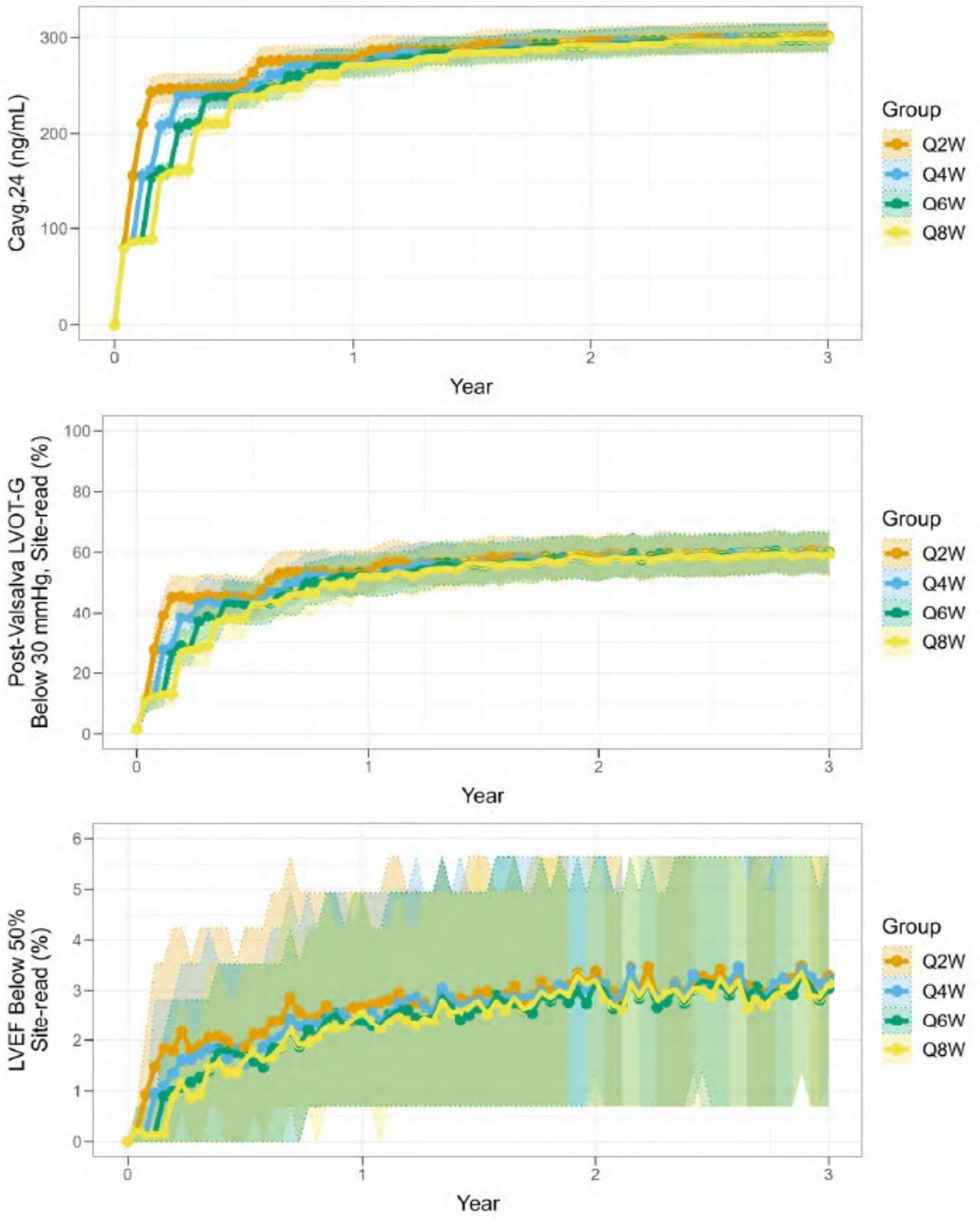


Figure 12. Proposed Commercial Dosing Regimen: Clinical Trial Simulation of Aficamten Exposure and Percent of Participants with Site-Read Post-Valsalva LVOT-G <30 mmHg or Site-Read LVEF < 50% over 3 Years of Daily Administration

Table 16. Proposed Commercial Dosing Regimen: Clinical Trial Simulation of Percent of Site-Read Post-Valsalva LVOT-G <30 mmHg over 3 Years of Daily Aficamten Administration

Week	Percent of Participants with LVOT-G < 30 mmHg [90% PI] per Monitoring Frequency			
	Q2W	Q4W	Q6W	Q8W
12	44.8 [38.0,51.4]	38.2 [31.7,45.1]	28.1 [22.5,33.8]	28.0 [21.8,33.8]
24	45.2 [38.0,52.1]	43.8 [37.3,50.7]	43.4 [35.9,50.0]	38.2 [31.7,45.1]
52	53.7 [46.5,60.6]	52.9 [45.8,59.9]	52.7 [45.8,59.2]	52.4 [45.1,59.2]
104	58.1 [50.7,64.8]	57.5 [50.7,64.1]	57.5 [50.7,64.1]	57.5 [50.7,64.1]
156	60.2 [52.8,66.9]	59.8 [53.5,66.9]	59.6 [52.8,66.2]	59.4 [52.1,65.5]

Abbreviations: LVOT-G = left ventricular outflow tract gradient; PI = prediction interval; QXW = one monitoring visit every X weeks.

Notes: The numbers represent simulation results for a virtual population of 10,000 participants. The prediction intervals indicate 5th to 95th percentiles for the percentage of participants on a given dose for 1000 simulations, each with 142 participants (size of Phase 3 study).

Table 17. Proposed Commercial Dosing Regimen: Clinical Trial Simulation of Percent of Site-Read LVEF <50% over 3 Years of Daily Aficamten Administration

Week	Percent of Participants with LVEF < 50% [90% PI] per Monitoring Frequency			
	Q2W	Q4W	Q6W	Q8W
12	2.2 [0.7,4.2]	1.6 [0.0,3.5]	1.1 [0.0,2.8]	1.1 [0.0,2.8]
24	1.8 [0.0,3.5]	1.8 [0.0,3.5]	1.8 [0.0,3.5]	1.4 [0.0,2.8]
52	2.7 [0.7,4.9]	2.4 [0.7,4.9]	2.4 [0.7,4.9]	2.6 [0.7,4.9]
104	3.4 [1.4,6.3]	3.2 [1.4,5.6]	3.1 [0.7,5.6]	3.2 [0.7,5.6]
156	3.3 [1.4,5.6]	3.2 [0.7,5.6]	3.0 [0.7,5.6]	3.1 [0.7,5.6]

Abbreviations: LVEF = left ventricular ejection fraction; PI = prediction interval; QXW = one monitoring visit every X weeks.

Notes: The numbers represent simulation results for a virtual population of 10,000 participants. The prediction intervals indicate 5th to 95th percentiles for the percentage of participants on a given dose for 1000 simulations, each with 142 participants (size of Phase 3 study).

Any difference in progression of LVOTG < 30 mmHg and LVEF < 50% between the evaluated dose titration frequencies appear small and limited to approximately the- first 6 months of treatment, supporting the appropriateness of a 2- to 8-week window for dose titration in the proposed commercial dose regimen. Furthermore, a larger window may also be useful in patients with pharmacodynamic interactions (see PK section), as this can increase half-life and time till steady state. Overall, aficamten dose titration appears to stabilize by approximately 2 years of administration with the proposed commercial dose regimen. A high probability of LVOT-G < 30 mmHg (approximately 60%) and low probability of LVEF < 50% (approximately 3%) would then be expected to persist.

2.6.5.2. Main study

CY 6031 (SEQUOIA-HCM)

Methods

CY 6031 was a phase 3, randomized, placebo-controlled, double-blind, multi-center trial in participants with symptomatic oHCM. Eligible participants were randomized in a 1:1 ratio to receive aficamten or placebo. Randomization was stratified by use of beta-blockers (yes or no) and cardiopulmonary exercise testing (CPET) exercise modality (treadmill or bicycle) and implemented in the interactive web response system. Enrollment limits were applied based on participant characteristics: participants taking beta-blockers were capped at approximately 70% of total enrollment; participants taking disopyramide were capped at approximately 10% of total enrollment; participants with persistent atrial fibrillation (AF) at screening were capped at approximately 15% of total enrollment; and participants using the bicycle CPET exercise modality were capped at approximately 50% of total enrollment. The trial comprised of three periods: screening, treatment, and a safety follow-up. Screening started after informed consent was signed; during this period of up to 6 weeks, assessments were performed to determine a participant's eligibility in the trial. The double-blind placebo-controlled treatment period lasted 24 weeks, after which there was a 4-week safety follow-up period without treatment. A cardiac magnetic resonance imaging sub-study was open to approximately 100 participants who consented to participate. An overview of the study schema is shown in Figure 13.

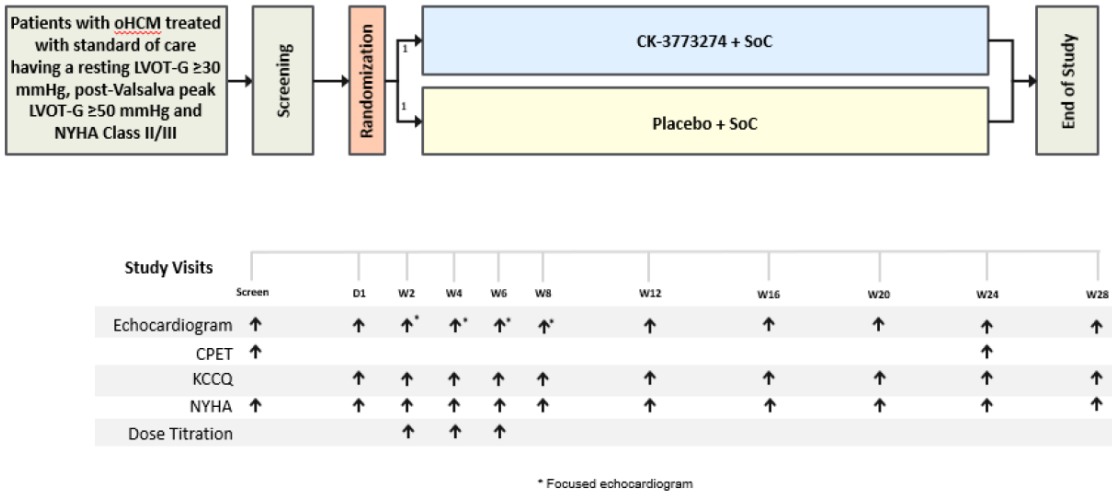


Figure 13. Study schema

- **Study Participants**

Patients were eligible to be included in the trial only if all the following criteria apply:

1. Males and females between 18 and 85 years of age, inclusive, at screening.
2. Body mass index <35 kg/m2.
3. Diagnosed with HCM per the following criteria:
    a. Has LV hypertrophy and non-dilated LV chamber in the absence of other cardiac disease and

b. Has an end-diastolic LV wall thickness as measured by the echocardiography core laboratory of:
· ≥15 mm in one or more myocardial segments OR
· ≥13 mm in one or more wall segments and a known-disease-causing gene mutation or positive family history of HCM

4. Has resting LVOT-G ≥30 mmHg and post-Valsalva LVOT-G ≥50 mmHg during screening as determined by the echocardiography core laboratory.
5. LVEF ≥60% at screening as determined by the echocardiography core laboratory.
6. New York Heart Association (NYHA) Functional Class II or III at screening
7. Hemoglobin ≥10 g/dL at screening.
8. Respiratory exchange ratio (RER) ≥1.05 and pVO2 ≤90% predicted on the screening CPET per the core laboratory.
9. Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on a stable regimen for >6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial. Patients treated with disopyramide must also be concomitantly treated with a beta blocker and/or calcium channel blocker.
10. Male participants must refrain from sperm donation during the trial and for 10 weeks afterward, and either remain abstinent or use a condom with their female partner, who must also use effective contraception if of childbearing potential. Female participants must not be pregnant, breastfeeding, or donating eggs, and if of childbearing potential, must use effective contraception during the trial and for 4 weeks afterward, with a negative pregnancy test before starting. Contraceptive use must follow study-specific guidelines and local regulations.

The following exclusion criteria were employed:

1. Significant valvular heart disease (per investigator judgment):
    a. Moderate-severe valvular aortic stenosis and/or regurgitation.
    b. Moderate-severe mitral regurgitation not due to systolic anterior motion of the mitral valve
2. Obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.
3. Known or suspected infiltrative, genetic or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis).
4. Prior treatment with cardiotoxic agents such as doxorubicin or similar.
5. History of LV systolic dysfunction (LVEF <45%) or stress cardiomyopathy at any time during their clinical course.
6. Has any ECG abnormality considered by the investigator to pose a risk to patient safety (eg, second degree atrioventricular block type II).
7. Documented paroxysmal atrial fibrillation during the screening period.
8. Paroxysmal or permanent atrial fibrillation is only excluded IF:
    a. rhythm restoring treatment (eg, direct-current cardioversion, atrial fibrillation ablation procedure, or antiarrhythmic therapy) has been required ≤6 months prior to screening

b. rate control and anticoagulation have not been achieved for at least 6 months prior to screening

9. History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.
10. ICD placement within 3 months prior to screening or planned ICD placement during the trial.
11. History of appropriate ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to screening.
12. Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or cannot postpone plans for septal reduction therapy until after the trial period.
13. Inability to exercise on a treadmill or bicycle (eg, orthopedic limitations).
14. Documented room air oxygen saturation reading <90% at screening.
15. 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. Patients with documented Gilbert syndrome and TBL ≥1.5 × ULN due to unconjugated hyperbilirubinemia, without other hepatic impairment, are permitted.
16. Recipient of a major organ transplant (eg, heart, lung, liver, bone marrow, renal) or anticipated transplantation within 12 months from randomization.
17. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 (by the modified Modification of Diet in Renal Disease equation) at screening.
18. Has received prior treatment with CK-3773274 or mavacamten.

CMR substudy

For the cardiac magnetic resonance sub-study, there were additional exclusion criteria, being 1) Inability to tolerate CMR, 2) Having an ICD, 3) having a cardiac pacemaker and 4) lack of consent for CMR sub-study.

Lifestyle Considerations

Patients will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests and before CPET. Patients should not exercise at all for 12 hours prior to CPET. Patients should also fast for at least 4 hours prior to CPET. Any medications that may cause drowsiness should be avoided for 8 hours prior CPET.

- **Treatments**

Aficamten or matching placebo tablets were to be taken orally, once daily, for 24 weeks. Aficamten was supplied as oral tablets containing 5 mg of aficamten; placebo was supplied as tablets matching the aficamten tablets. Aficamten and matching placebo tablets were packaged in blister packs, which were labelled per country-specific requirements. Tablets (both aficamten and placebo) were manufactured by a vendor. Study drug lot numbers were as follows:

• Aficamten 5 mg tablets: CKPGB, CKPGC, and CKTCN

• Placebo for aficamten tablets: CHVZV

Investigational product was packaged in blister strips that contained either 5 mg tablets of aficamten or matching placebo, which were then supplied to participants within a blister card that contained 4

blister strips. Each blister card contained a combination of active and/or placebo strips to provide the correct dose.

Dose titration

Participants randomized to aficamten could have received up to 4 escalating doses of aficamten over the initial 6 weeks of the trial (at week 2, 4, and 6). Participants receiving aficamten started at a dose of 5 mg once daily (dose 1) and could have escalated to doses of 10, 15, and 20 mg once daily if they met the escalation criteria; if the dose escalation criteria were not met, participants stopped escalation and were maintained at their current dose. At the Week 2 visit, each participant had an echocardiogram 2 hours following administration of their aficamten dose. The dose was up-titrated to dose 2 if on the echo valsalva LVOT-G ≥ 30 mmHg and the biplane LVEF ≥ 55%, otherwise, the participant remained on dose 1. If LVEF was < 50% at week 2, the IWRS assigned the participant to placebo.

At the week 4 visit, the dose was up-titrated to the next higher dose if on the echo valsalva LVOT-G ≥ 30 mmHg and the biplane LVEF ≥ 55%, otherwise, the participant remained on the same dose. If LVEF was <50% at week 4, the IWRS assigned the participant to the prior dose level or to placebo if the participant was on dose 1. At the week 6, the dose was up-titrated to the next higher dose if on the echo the valsalva LVOT-G ≥ 30 mmHg and the biplane LVEF ≥ 55%, otherwise, the participant remained on the same dose. If LVEF was < 50% at Week 6, the IWRS assigned the participant to the prior dose level or to placebo if the participant was on dose 1. Once a participant's aficamten dose was down titrated, no further escalation was permitted.

At the Week 8 visit, each participant had an echocardiogram to ensure the LVEF was ≥ 50%. If the LVEF was <50% at week 8, the IWRS assigned the participant to the next lower dose or to placebo if the participant was on dose 1. The titration criteria are shown in Table 20.

Table 18. Echocardiogram Criteria for Scheduled Dose Titrations

Biplane LVEF		Valsalva LVOT-G	Action
< 50%			Reduce Dose[a]
≥ 50% - 55%			No Dose Change
≥ 55%	and	< 30 mmHg	No Dose Change
≥ 55%	and	≥ 30 mmHg	Increase Dose

IP = investigational product; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient

[a] Once a participant's IP dose was down titrated, no further escalation was permitted. If LVEF was < 50% on 5 mg, the participant received placebo.

Dose Reduction

After week 6, no dose escalations were allowed. During the study, for safety reasons, dose reductions could have occurred at scheduled or unscheduled visits. Dose reductions were determined by the IWRS based on echocardiography results. After week 8, dose reductions were based on echocardiogram results from the initial scheduled or unscheduled visits. If the LVEF was < 50%, then the IWRS assigned the participant to the next lower dose or to placebo if the participant was on Dose 1. The IWRS did not further reduce the dose for at least 7 days after the previous reduction.

Dose interruption

A temporary treatment interruption was implemented when a predefined safety threshold (see LVEF<40% below) was met or was considered by the investigator in the case of an AE/SAE or for another reason. If a temporary treatment interruption occurred because a safety threshold was met, blinded treatment was resumed at least 7 days later, either at a lower dose or with a permanent switch to placebo if the participant was at 5 mg. If the treatment was temporarily interrupted because of an AE/SAE, the investigator was to make the best effort to resume treatment as soon as practically possible, assuming there were no remaining safety concerns. If dosing was interrupted for more than 3 consecutive days in the first 6 weeks and more than 7 consecutive days thereafter, the investigator was to contact the Medical Monitor to discuss the participant. All temporary IP interruptions of greater than 3 days were recorded in the electronic case report form (CRF) (stop and start dates and reason for interruption).

LVEF<40%

If the unblinded echocardiologist observes that the LVEF has crossed the defined safety threshold of <40% or feels the patient requires urgent medical attention, the unblinded echocardiologist will enter the LVEF value in the IWRS and discuss the results with the blinded investigator or qualified designee. The Medical Monitor will be informed in these cases. If a patient's LVEF is <40% at any time, the following steps should occur after consultation with the Medical Monitor:

• The investigational product should be stopped and held for at least 7 days.

• Repeat echocardiograms should be performed per investigator judgment until a normal LVEF (≥55%) has been documented at which point the patient can be restarted on investigational product after being down-titrated.

Other medication

Participants could continue to take prescription medications that in the opinion of the investigator and the Medical Monitor would not interfere with the study. During the trial, medications and doses were to remain stable whenever appropriate. Participants on beta-blockers, verapamil, diltiazem, or disopyramide should have been on stable doses for > 6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial. Participants treated with disopyramide must have been concomitantly treated with a beta blocker and/or calcium channel blocker. Doses were individually optimized based on local practice. Per protocol, administration of aficamten with strong cytochrome P450 3A inhibitors or inducers or with known substrates of P-glycoprotein was to proceed with caution due to incomplete availability of drug-drug interaction data.

The use of rescue medications in the event of a low cardiac output was allowed at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication were to be recorded.

- **Objectives and endpoints**

The primary objective of CY 6031 was to evaluate the effect of aficamten on exercise capacity in participants with symptomatic oHCM. The corresponding endpoint was change in pVO2 by CPET from baseline to Week 24. Comparison was made of the aficamten group to the placebo group, with the hypothesis that there is superiority of aficamten over placebo on the primary endpoint. An overview of all objectives and endpoints used in CY 6031 is shown in Table 21.

Table 19. Objectives and endpoints of CY 6031.

Objectives	Endpoint(s)
Primary	
To evaluate the effect of aficamten on exercise capacity in participants with symptomatic oHCM	• Change in pVO2 by CPET from baseline to Week 24
Secondary	
To evaluate the effect of aficamten on participant health status	• Change in KCCQ-CSS from baseline to Week 12 and Week 24
To evaluate the effect of aficamten on NYHA Functional Classification	• Proportion of participants with ≥ 1 class improvement in NYHA Functional Class from baseline to Week 12 and Week 24
To evaluate the effect of aficamten on Valsalva LVOT-G	• Change in Valsalva LVOT-G from baseline to Week 12 and Week 24 • Proportion of participants with Valsalva LVOT-G < 30 mmHg at Week 12 and Week 24
To evaluate the effect of aficamten on duration of eligibility for SRT	• Duration of eligibility for SRT during the 24-week treatment period in participants who were eligible for SRT at baseline
To evaluate the effect of aficamten on exercise capacity	• Change in total workload during CPET from baseline to Week 24
Safety	
To evaluate the safety and tolerability profile of aficamten in participants with symptomatic oHCM	• Incidence of reported major adverse cardiac events (CV death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization) • Incidence of new onset persistent AF • Incidence of appropriate ICD discharges and aborted sudden cardiac death • Incidence of LVEF < 50% • Incidence of LVEF < 50% with at least 1 of the following: – Signs and symptoms of heart failure (concomitant AE of heart failure or dyspnea) AND/OR – Increase in NT-proBNP (≥ 30% increase) relative to results from the most recent previous visit and above the ULN at the time of LVEF assessment < 50% • Incidence of TEAEs

Exploratory	
To evaluate the effect of aficamten on exercise capacity and functional class	• Compared with baseline, proportion of participants at Week 24 achieving either: – Change from baseline of ≥ 1.5 mL/kg/min in pVO_2 AND ≥ 1 class improvement in NYHA Functional Class **OR** – Change from baseline of ≥ 3.0 mL/kg/min in pVO_2 AND no worsening of NYHA Functional Class
To evaluate the effect of aficamten on participant response over time	• Proportion of participants with improvement in KCCQ-CSS ≥ 5 points at Weeks 12 and 24 • Proportion of participants with resting LVOT-G < 30 mmHg, Valsalva LVOT-G < 50 mmHg, and NYHA Functional Class I at Weeks 12 and 24 • Proportion of participants with resting LVOT-G < 30 mmHg, Valsalva LVOT-G < 50 mmHg, and ≥ 1 class improvement in NYHA Functional Class at Weeks 12 and 24
To evaluate the effect of aficamten on SRT eligibility	• Proportion of participants who are eligible for SRT at Week 24 among participants who were eligible for SRT at baseline
To evaluate the effect of aficamten on other CPET parameters	Change from baseline to Week 24 in: • Ventilatory efficiency (VE/VCO_2 slope) • Circulatory power (VO_2 × systolic BP) • VAT
To evaluate the effect of aficamten on health status and health-related quality of life as measured by PRO questionnaire	• Change from baseline to Week 24 in individual responses to the EQ-5D-5L instrument
To evaluate the effect of aficamten on health status and quality of life related to chest pain-like angina	• Change from baseline to Week 24 in summary and domain scores for the SAQ-7
To evaluate the effect of aficamten on cardiac function and structure	• Change from baseline to Week 24 in echocardiographic measurements of cardiac structure and of systolic function including: – LVEF – LVESV and LVEDV – Left atrial volume
To evaluate the effect of aficamten on biomarker levels	• Change from baseline values in NT-pro-BNP, hs-cTnI and other biomarkers through Week 24
To evaluate the effect of aficamten on left ventricular mass, function, and structure by CMR imaging	• Change from baseline to Week 24 in CMR measurements of: – LV mass index – LVEF – Septal, free wall, and maximal wall thickness – Left atrial volume index – LVESV – LVEDV
To assess the PK of aficamten and its metabolites	• PK parameters through Week 24

AE = adverse event; AF = atrial fibrillation; BP = blood pressure; CMR = cardiac magnetic resonance; CPET = cardiopulmonary exercise testing; CV = cardiovascular; EQ-5D-5L = EuroQol 5-dimension 5-level; hs-cTnI = high sensitivity cardiac troponin I; ICD = implantable cardiac defibrillator; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVOT-G = left ventricular outflow tract gradient; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; PK = pharmacokinetic(s); PRO = patient-reported outcome; pVO_2 = peak oxygen uptake; SAQ-7 = Seattle Angina Questionnaire-7; SRT = septal reduction therapy; TEAE = treatment-emergent adverse event; ULN = upper limit of normal; VAT = ventilatory anaerobic threshold; VCO_2 = volume of exhaled carbon dioxide; VE = ventilation

The primary endpoint is change in pVO2 from baseline to Week 24. The primary analysis will be performed using an ANCOVA model that includes terms of treatment, randomization stratification factors (beta-blocker use status and CPET modality), baseline pVO2 and baseline body weight as covariates in the FAS. Subjects will be followed per the schedule of assessments from randomization through their final visit irrespective of whether the subject is continuing to receive study treatment. Reasons for not completing Week 24 CPET will be recorded on eCRF; categories of reasons include adverse events, early termination, equipment failure, investigator decision, subject decision and other. The percentage of missing CPET data at Week 24 and the reasons for the missing data will be tabulated in the FAS. The following type of intercurrent events could preclude CPET at Week 24: Death, hospitalization, CV AEs, non-CV AEs (e.g., orthopedic injury) and COVID-19 related intercurrent events e.g., subjects' decision to early terminate from the study due to the COVID-19 precautions, site closures, hospitalization due to COVID-19, or COVID-19 symptoms preventing subjects from coming to the Week 24 visit. Missing Week 24 CPET due to intercurrent events i.e., non-CV AEs or COVID-19 related intercurrent events will be considered as MAR. It is unclear how many patients had data after on CPET after an intercurrent event. The current description implies that a hypothetical strategy was used. The estimand is for the primary endpoint is shown in Table 22.

Table 20. Estimands for primary objective

Population	**Patients with symptomatic obstructive hypertrophic cardiomyopathy having NYHA class II and III**
Treatment condition<s>	Aficamten in addition to standard of care, regardless of discontinuation, compared to placebo in addition to standard of care, regardless of discontinuation.
Endpoint (variable)	Change from baseline to Week 24 in pVO2.
Population-level summary	Difference in mean change from baseline to week 24 between the aficamten and placebo group
Intercurrent events and strategy to handle them	
Death, Hospitalization, CV AE's, non-CV AEs, COVID-19 related intercurrent events	Not reported. Missing pVO2 at Week 24 will be imputed using multiple imputation methodology under the MAR assumption. Appears to be a hypothetical strategy, although not specified clearly in the protocol or SAP.
CPET core lab flags CPET as invalid	Not reported. Invalid pVO2 Week 24 will be imputed using multiple imputation methodology under the MAR assumption. Appears to be a hypothetical strategy, although not specified clearly in the protocol or SAP.
Treatment discontinuation	Not reported, likely hypothetical strategy.

- **Sample size**

Sample size calculation was based on the assumptions of change from baseline in pVO2 of 1.5 mL/kg/min for aficantem compared to placebo and a standard deviation (SD) of 3.5 mL/kg/min. At randomization ratio of 1:1 (approximately 135 randomized to aficantem and 135 randomized to placebo) provides more than 90% power to detect the difference in pVO_2 change from baseline to Week 24 with a 2-sided type I error of 0.05.

- **Randomisation and Blinding (masking)**

This was a double-blind study. All eligible participants were centrally assigned to randomized investigational product using the interactive web response system (IWRS). Participants, investigators, study site personnel, the study coordinator, and the sponsor were blinded to treatment assignment.

Because viewing echocardiogram results could have potentially compromised the blinded investigator and blinded study coordinator, only an unmasked sonographer and unmasked echocardiologist (or unmasked data entry designee) were allowed access to echocardiogram images or results for the study. An unmasked sonographer at the site performed the echocardiograms. An unmasked cardiologist, who was not the investigator and was designated as the unmasked echocardiologist, read the echocardiograms, measured the LVOT-G and LVEF and entered the echocardiogram results in the IWRS for dose titrations and adjustments. An unmasked designee, who was also not involved in other aspects of the study visits, was allowed to enter data into the IWRS on the unmasked chocardiologist's behalf. Except in the event of a critical safety issue (eg, LVEF < 40%), neither the unmasked echocardiologist nor the unmasked data entry designee were allowed to convey echocardiogram results to the rest of the study team. All site staff, including the unmasked echocardiologist and the unmasked designee, remained blinded to randomized treatment assignments throughout the study. There was a similar masking requirement for the NT-proBNP results. NT-proBNP results were to be masked to all site personnel. NT-proBNP was not to be tested in local laboratories unless medically necessary. If results were available from local laboratories, the principal investigator and study team were to avoid accessing these data.

All eligible patients will be centrally assigned to randomized aficamten using the IWRS. Randomization will be stratified by use of beta-blockers (yes or no) and CPET exercise modality (treadmill or bicycle) and implemented in the IWRS.

- **Statistical methods**

The primary analysis for the primary endpoint was to be performed using an ANCOVA model that includes treatment group, randomization stratification factors (beta-blockers use status and CPET modality), baseline pVO_2 and baseline body weight. The primary estimand was planned to be a FAS estimand that would focus on estimating treatment difference regardless of completing 24 weeks of treatment and experiencing ICEs. The secondary estimand was planned to be the hypothetical one where the subjects with missing week 24 pVO_2 due to ICEs or discontinuing treatment prior to week 24 would be excluded.

Missing pVO2 at Week 24 regardless of type of intercurrent events was to be imputed using multiple imputation methodology under the MAR assumption for the primary analysis of the primary estimand.

A regression model where treatment group, randomization stratification factors, baseline pVO_2 sex, age, baseline hemoglobin, baseline body weight, baseline KCCQ CSS, baseline NYHA class and last available post randomization NYHA functional class, resting and Valsalva LVOT was planned to be used

for imputation. After generating one hundred imputed dataset and analysing each imputed dataset using the primary analysis model, Rubin's rules were to be used to combine LSM estimate of treatment difference and the standard error to produce a LSM estimate of the treatment difference, its 95% confidence interval, and p-value for the test of null hypothesis of no treatment effect.

Apart from the stratification factors, it is also planned that the following covariates were to be tested as confounders and effect modifiers: sex, age group, baseline BMI, baseline NYHA class, baseline KCCQ CSS, baseline LVEF, baseline NT-proBNP, CPET modality, beta blocker use, baseline resting LVOT, sarcomric gene mutation status.

Sensitivity analysis was also planned using placebo based imputation and tipping point analysis. In placebo-based imputation, missing pVO_2 from subjects who discontinued to aficamten treatment or missing pVO2 from subjects from the placebo arm were to be imputed based on the model that was constructed using observed pVO_2 data from the placebo arm. Missing pVO_2 from subjects who remained on aficamten treatment were planned to be imputed based on a model that is constructed using observed pVO2 data from aficamten arm.

Tipping point analysis were planned to adjust the imputed value of missing pVO2 in aficamten group by applying a range of negative shift values. If more than 10% of the subjects had missing data and/or more than 5% of the subjects had missing data due to reason related to IP, the primary analysis were to be missing data imputed using placebo-based imputation.

Another sensitivity analysis was also planned using a repeated measures mixed model to pVO_2 baseline and Week 24 data. The RMMM were to include stratification factors, visit, stratification by visit, and a numeric covariate which equals 0 for both treatment groups at baseline and equals 0 for placebo at Week 24 and equals 1 for aficamten group at Week 24.

Another sensitivity analysis to evaluate the impact of COVID-19 was planned. In those analysis primary analysis were to be repeated after setting the Week 24 CPET to missing from subjects who are impacted by COVID pandemic.

In the estimands for secondary endpoints, intercurrent events were 'study discontinuation' and 'assessment not performed', which were handled by a mix of treatment policy (when data was observed) and hypothetical strategy (when missing). Analysis of secondary endpoints were planned to be performed using repeated measures mixed model for continuous endpoints (using baseline as a covariate, randomization stratification factors, visit, treatment group, treatment group by visit interaction and baseline by visit interaction) or an ANCOVA model (for total duration of SRT eligible during the 24 week of treatment period only) and using Cochran-Mantel-Haenszel test for categorical endpoints (stratified by randomization factors).

Results

- **Recruitment**

The date first participant enrolled was 01 February 2022 and the date last participant completed was 18 December 2023. A total of 543 persons were screened for the study. Of these, 261 failed screening, primarily for not satisfying the inclusion/exclusion criteria (98.9%). The entry criteria that were most frequently not met were a resting LVOT-G $\geq$ 30 mmHg and Valsalva LVOT-G $\geq$ 50 mmHg as determined by the echocardiography core laboratory (n = 113) and an RER $\geq$1.05 and pVO2 $\leq$ 90% predicted (n = 82).

A total of 282 eligible participants were included at 82 centers in 14 countries. A total of 46 were from China, 94 from North America and 142 from other parts of the world. In Europe there were 4 from Portugal, 17 from Poland, 7 from Netherlands, 12 from Italy, 7 from Hungary, 18 from UK, 17 from France, 32 from Spain, 11 from Germany, 7 from Denmark and 1 from the Czech Republic.

- **Participant flow**

The enrolled participants (n=282) were randomized to treatment as follows: 142 to aficamten and 140 to placebo. All participants in both treatment groups received at least 1 dose of investigational product. Of the participants randomized to aficamten, 5 (3.5%) discontinued treatment early: 2 due to participant withdrawal, 2 due to a protocol deviation, and 1 due to an AE. Of the participants randomized to placebo, 4 (2.9%) discontinued treatment early: 2 due to an AE, 1 due to physician decision, and 1 due to other (COVID-19 restrictions), see Table 23 and Figure 14.

Table 21. Participant Disposition (All Randomized Set)

	Aficamten (N=142) n (%)	Placebo (N=140) n (%)	Overall (N=282) n (%)
Participants received at least 1 dose	142 (100)	140 (100)	282 (100)
Participants completed treatment[a]	137 (96.5)	136 (97.1)	273 (96.8)
Participants early terminated from treatment[a]	5 (3.5)	4 (2.9)	9 (3.2)
Reason for early termination from treatment[b]			
Physician decision	0	1 (25.0)	1 (11.1)
Adverse event	1 (20.0)	2 (50.0)	3 (33.3)
Withdrawal by participant	2 (40.0)	0	2 (22.2)
Protocol deviation	2 (40.0)	0	2 (22.2)
Other	0	1 (25.0)	1 (11.1)
Participants completed study[a]	139 (97.9)	137 (97.9)	276 (97.9)
Participants early terminated from study[a]	3 (2.1)	3 (2.1)	6 (2.1)
Reason for early termination from study[c]			
Physician decision	0	2 (66.7)	2 (33.3)
Adverse event	0	1 (33.3)	1 (16.7)
Withdrawal by participant	2 (66.7)	0	2 (33.3)
Other	1 (33.3)	0	1 (16.7)

[a] Percentages were calculated using the number of participants who received at least 1 dose as denominator.
[b] Percentages were calculated using the number of participants who terminated treatment early as denominator.
[c] Percentages were calculated using the number of participants who terminated the study early as denominator.

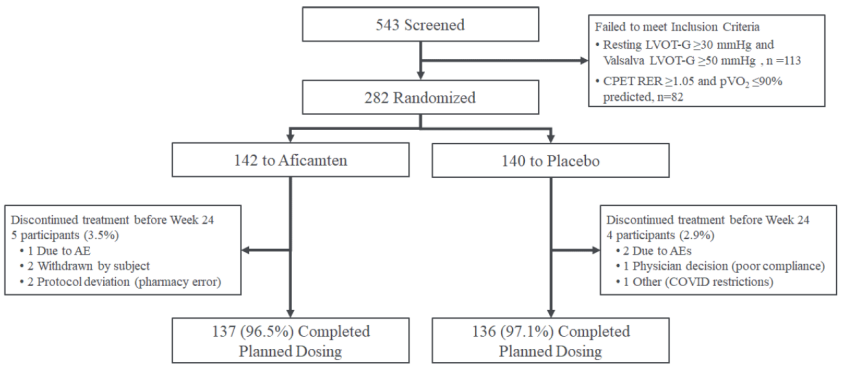


Figure 14. Participant flow.

Analyses sets:

The full analyses set was used for analyses of efficacy/PD; the safety analysis set was used for analyses of demographics, exposure, and safety; and the PK Analysis Set for PK analyses. Each of these 3 analysis sets consisted of all 282 dosed participants, with 142 participants in the aficamten group and 140 participants in the placebo group, definitions are shown in Table 24.

Table 22. Analysis Sets

Analysis Set	Definition
All Screened Participants	Included all participants who signed an ICF
Randomized Participants	Included all participants randomized to receive aficamten or placebo
Safety Analysis Set	Included all randomized participants who received at least 1 dose of IP, aficamten or placebo
Full Analysis Set	Included all randomized participants
Pharmacokinetics Analysis Set	Included all dosed participants who had at least 1 evaluable plasma concentration sample, provided they had no major protocol violations/deviations that could have affected the PK of aficamten

ICF = informed consent form; IP = investigational product; PK = pharmacokinetic(s)

Treatment exposure:

Participants treated with aficamten received treatment for a median of 169.0 days and had a median cumulative total exposure of 2384.4 mg. Participants treated with placebo received treatment for a median of 170.0 days.

Of the 142 participants treated with aficamten, 68 (48.6%) achieved an aficamten dose of 20 mg daily at Week 8; of these participants, 3 were subsequently down-titrated to 15 mg daily, and no participant had a further dose reduction. A total of 49 participants (35.0%) achieved an aficamten dose of 15 mg daily at Week 8, and 3 were subsequently down-titrated to 10 mg daily, with no further dose reductions. The Week 8 aficamten dose was 10 mg daily for 18 participants (12.9%) and 5 mg daily for 5 participants (3.6%); no dose reductions occurred for participants at either of these dose levels. Two participants discontinued treatment prior to Week 8 (due to participant withdrawal from the study); 1 participant had been titrated to 15 mg daily prior to discontinuation of treatment, and 1 participant had been titrated to 10 mg daily prior to discontinuation of treatment (Table 25).

Table 23. Summary of aficamten dose achieved by visit

	Aficamten Dose Achieved					
Visit	0 mg n (%)	5 mg n (%)	10 mg n (%)	15 mg n (%)	20 mg n (%)	Overall n (%)
Day 1	0	142 (100)	—	—	—	142
Week 2	0	21 (14.8)	121 (85.2)	—	—	142
Week 4	0	8 (5.7)	35 (24.8)	98 (69.5)	—	141
Week 6	0	5 (3.6)	17 (12.1)	50 (35.7)	68 (48.6)	140
Week 8	0	5 (3.6)	18 (12.9)	49 (35.0)	68 (48.6)	140
Week 12	0	5 (3.6)	19 (13.7)	48 (34.5)	67 (48.2)	139
Week 16	0	5 (3.6)	21 (15.2)	48 (34.8)	64 (46.4)	138
Week 20	0	5 (3.6)	21 (15.3)	48 (35.0)	63 (46.0)	137
Week 24	0	5 (3.6)	21 (15.3)	48 (35.0)	63 (46.0)	137

Note: Doses achieved were doses assigned by the interactive web response system.

- **Conduct of the study**

The original protocol was dated 26 July 2021, and there were 4 protocol amendments; key changes in each amendment are described in Table 26.

Table 24. Protocol amendments CY 6031.

Amendment	Description of Change
Amendment 01 17 August 2021	• Revised eligibility criteria to include participants with a wall thickness ≥ 13 mm in one or more wall segments and a known disease-causing gene mutation or positive family history of HCM • Corrected exclusion criterion to state that participants with an oxygen saturation < 90% were not eligible for the study • Clarified that eligibility criteria for the CMR sub-study were exclusion criteria
Amendment 01 CHN 03 November 2021	• Clarify Ji Xing responsibilities in China • Updated administrative information (ie, key contact information, CHN protocol versioning, Medical Monitor signatory) • Removed references to Clinical Laboratory Improvement Amendments (CLIA) certified laboratory testing for genetic testing • Removed description of access to investigational product at the end of the study
Amendment 02 10 December 2021	• Allowed enrollment of participants taking disopyramide; clarified enrollment criteria for participants taking disopyramide; and added enrollment cap for participants taking disopyramide • Increased the number of participants in the CMR sub-study to ensure appropriate power; clarified CMR requirements; and clarified CMR testing window at the end of treatment • Added lifestyle restrictions prior to CPET • Modified the schedule of activities: removed PGI-C and Day 1 and Week 28, removed CGI at Day 1, added EQ-5D-5L timing to align with those of KCCQ and NYHA, removed medical/surgical history at Day 1, added more frequent pregnancy testing, added collection of plasma for future analysis, and added an option to split the Week 24 visit over 2 days
Amendment 02 CHN 14 January 2022	• Incorporated changes from global Amendment 02, with the exception of collection of plasma for future analysis
Amendment 03 03 January 2023	• Added endpoints to evaluate the duration of time that participants were eligible for SRT • Updated pVO_2 criterion to allow for participants with higher predicted pVO_2 • Added the option to increase the sample size (based on pVO_2 variability and missing data rate) to maintain the intended power • Clarified that designated site staff who were unmasked to echocardiogram results remained blinded to participant treatment assignments
Amendment 03 CHN 14 March 2023	• Incorporated changes from global Amendment 03 • Reinstated description of access to investigational product at the end of the study
Amendment	**Description of Change**
Amendment 04 08 December 2023	• Added the safety endpoint of incidence of LVEF < 50% with signs and symptoms of heart failure (concomitant AE of heart failure or dyspnea) and/or increase in NT-proBNP from baseline • Updated the definition of the FAS to include all randomized participants • Simplified the testing hierarchy from a parallel gatekeeping method to a closed testing procedure

CGI = clinical global impression; CMR = cardiac magnetic resonance; CPET = cardiopulmonary exercise testing; EQ-5D-5L = EuroQol 5-dimension 5-level; FAS = Full Analysis Set; HCM = hypertrophic cardiomyopathy; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI-C = Patient Global Impression of Change; pVO_2 = peak oxygen uptake; SRT = septal reduction therapy

Protocol violations

The conservative approach to classification of protocol deviations performed during the study resulted in a total of 705 major protocol deviations for 223 participants (79.1%): 109 participants (76.8%) in the aficamten group and 114 participants (81.4%) in the placebo group. A cross-functional review of the protocol deviations after database lock and unblinding was performed to adjudicate their severity according to the ICH definition of important, consistent with the SOP and SAP wording. While the original classification of major was not changed, major protocol deviations were further classified as important or not important per the ICH E3 definition. If a protocol deviation category originally

classified as major was assessed as not important, a rationale was provided. For protocol deviation categories that could not be readily classified as important or not important as a whole due to variability of severity within the category, each protocol deviation record was reviewed and assigned an individual classification based on severity; during this record review, reviewers were not provided the treatment assignments. Application of the important protocol deviation classification to the major protocol deviation dataset yielded 62 important protocol deviations for a total of 51 participants (18.1%): 24 participants (16.9%) in the aficamten group and 27 participants (19.3%) in the placebo group. The incidence of important protocol deviations was similar between the aficamten and placebo groups for all category subtypes.

Table 25. Major protocol violations

Protocol Deviation Type	Aficamten (N=142)	Placebo (N=140)	Overall (N=282)
Any Major Protocol Deviation	109 (76.8)	114 (81.4)	223 (79.1)
Procedures	70 (49.3)	72 (51.4)	142 (50.4)
IP Administration/Study Treatment	67 (47.2)	58 (41.4)	125 (44.3)
Informed Consent	35 (24.6)	40 (28.6)	75 (26.6)
Visit Schedule	15 (10.6)	15 (10.7)	30 (10.6)
Laboratory Tests	11 (7.7)	14 (10.0)	25 (8.9)
Other	4 (2.8)	3 (2.1)	7 (2.5)
AE/SAE	3 (2.1)	3 (2.1)	6 (2.1)

AE = adverse event; IP = investigational product; SAE = serious adverse event
Note: Participants were counted once for each row if multiple protocol deviations were reported.

- **Baseline data**

Overall, participants had a median age of 59.5 years, with a range of 18 to 84 years. Most participants were male (59.2%), white (79.1%), and not Hispanic or Latino (91.5%). Overall, approximately half of the participants were in either North America (33.3%) or China (16.3%); the remaining participants were included in the "rest of world", which most frequently (> 5%) included Spain (11.3%), the United Kingdom (6.4%), France (6.0%), and Poland (6.0%). Demographic characteristics were generally balanced between the aficamten and placebo treatment groups (Table 28).

Table 26. Demographics

	Aficamten (N=142)	Placebo (N=140)	Overall (N=282)
Age (Years)			
Mean (SD)	59.2 (12.55)	59.0 (13.37)	59.1 (12.94)
Median	59.0	60.0	59.5
Min, Max	18, 83	23, 84	18, 84
Sex, n (%)			
Male	86 (60.6)	81 (57.9)	167 (59.2)
Female	56 (39.4)	59 (42.1)	115 (40.8)
Race, n (%)			
White	108 (76.1)	115 (82.1)	223 (79.1)
Black or African American	3 (2.1)	0	3 (1.1)
Asian	29 (20.4)	25 (17.9)	54 (19.1)
Other	2 (1.4)	0	2 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	3 (2.1)	6 (4.3)	9 (3.2)
Not Hispanic or Latino	128 (90.1)	130 (92.9)	258 (91.5)
Not reported	11 (7.7)	4 (2.9)	15 (5.3)
Region			
North America	49 (34.5)	45 (32.1)	94 (33.3)
China	24 (16.9)	22 (15.7)	46 (16.3)
Rest of World	69 (48.6)	73 (52.1)	142 (50.4)

SD = standard deviation

Baseline characteristics are shown in Table 29. At baseline, participants had a median BMI of 28.1 kg/m2. The majority of participants had NYHA Class II heart failure (75.9%). The mean LVEF was 74.8%, the mean resting LVOT-G was 55.1 mmHg, and the mean Valsalva LVOT-G was 83.1 mmHg (all echocardiographic data were reported from the core laboratory assessment unless noted otherwise). A total of 61 participants (32 aficamten, 29 placebo) were SRT eligible at baseline (defined as having NYHA Class III or IV heart failure and a resting or Valsalva LVOT-G ≥ 50 mmHg). The mean pVO2 by CPET at baseline was 18.5 mL/kg/min, with 55% of participants using treadmill as the CPET modality.

Table 27. Baseline characteristics CY 6031

Baseline Assessments	Aficamten (N=142)	Placebo (N=140)	Overall (N=282)
BMI (kg/m²)			
Mean (SD)	28.0 (3.76)	28.2 (3.75)	28.1 (3.75)
Median (Min, Max)	28.1 (18, 35)	28.2 (19, 35)	28.1 (18, 35)
NYHA Class at Baseline, n (%)			
Class II	108 (76.1)	106 (75.7)	214 (75.9)
Class III	34 (23.9)	33 (23.6)	67 (23.8)
Class IV	0	1 (0.7)	1 (0.4)
SRT Eligibility, n (%)	32 (22.5)	29 (20.7)	61 (21.6)
CPET Modality at Baseline, n (%)			
Bicycle	64 (45.1)	63 (45.0)	127 (45.0)
Treadmill	78 (54.9)	77 (55.0)	155 (55.0)
Resting LVOT-G (mmHg) [a]			
Mean (SD)	54.8 (27.02)	55.3 (32.15)	55.1 (29.63)
Median (Min, Max)	50.7 (12, 147)	52.1 (8, 155)	51.1 (8, 155)
Valsalva LVOT-G (mmHg) [a]			
Mean (SD)	82.9 (32.00)	83.3 (32.68)	83.1 (32.28)
Median (Min, Max)	83.5 (15, 246)	79.7 (11, 194)	81.4 (11, 246)
NT-proBNP (ng/L)			
Geo Mean (Geo CV%)	734.7 (170.63)	709.8 (160.78)	722.2 (165.18)
Median (Min, Max)	818.0 (13, 16115)	691.5 (36, 6086)	788.0 (13, 16115)
LVEF (%) [a]			
Mean (SD)	74.8 (5.48)	74.8 (6.26)	74.8 (5.87)
Median (Min, Max)	75.2 (56, 87)	75.8 (51, 87)	75.6 (51, 87)
pVO_2 at Baseline CPET (mL/kg/min)			
Mean (SD)	18.4 (4.45)	18.6 (4.51)	18.5 (4.47)
Median (Min, Max)	18.3 (9, 31)	18.5 (9, 32)	18.4 (9, 32)
KCCQ-CSS			
Mean (SD)	75.6 (18.42)	73.7 (17.55)	74.7 (17.99)
Median (Min, Max)	79.9 (11, 100)	76.6 (26, 100)	78.1 (11, 100)
Systolic BP (mmHg) at Baseline			
Mean (SD)	124.6 (15.90)	125.7 (16.02)	125.2 (15.94)
Median (Min, Max)	123.5 (84, 166)	124.0 (84, 172)	124.0 (84, 172)
Diastolic BP (mmHg) at Baseline			
Mean (SD)	74.6 (10.70)	74.1 (10.58)	74.4 (10.63)
Median (Min, Max)	74.0 (48, 102)	74.0 (42, 119)	74.0 (42, 119)
Heart rate (beats/minute) at Baseline			
Mean (SD)	65.5 (10.56)	65.6 (11.93)	65.6 (11.24)
Median (Min, Max)	64.0 (41, 92)	64.0 (43, 102)	64.0 (41, 102)

Hypertrophic Cardiomyopathy and Select Cardiovascular Histories and Procedures

All participants had LV hypertrophy and a non-dilated LV chamber in the absence of other cardiac disease at the time of enrollment. Overall, 26.6% of participants had a family history of HCM, and 17.4% of participants had a known HCM-causing gene mutation (per medical history assessment) at enrollment. The median time since the initial HCM diagnosis was 4.07 years (range: 0.0–45.9 years).

Selected CV history most frequently included paroxysmal AF (14.5%), coronary artery disease (12.4%), and cardiac syncope (11.3%). Insertion of an implantable cardioverter defibrillator was the

most common prior CV procedure (13.8% of participants overall). Cardiovascular histories and procedures were similar between the aficamten and placebo groups, see Table 30.

Frequently reported medical histories overall included hypertension (including essential hypertension, 51.4% of participants overall), hyperlipidemia (27.0%), gastroesophageal reflux disease (13.1%), hypercholesterolemia (12.8%), and dyslipidemia (11.7%). Medical history according to treatment arm is shown in Table 31.

Table 28. Summary of HCM History, Select Cardiovascular History, and Cardiovascular Procedures

	Aficamten (N=142)	Placebo (N=140)	Overall (N=282)
Obstructive HCM criteria, n (%)			
LV hypertrophy and non-dilated LV chamber in the absence of other cardiac disease	142 (100)	140 (100)	282 (100)
Positive family history of HCM	41 (28.9)	34 (24.3)	75 (26.6)
Known HCM-causing gene mutation	24 (16.9)	25 (17.9)	49 (17.4)
HCM morphology, n (%)			
Isolated basal septal hypertrophy	78 (54.9)	63 (45.0)	141 (50.0)
Reverse septal curvature	22 (15.5)	34 (24.3)	56 (19.9)
Apical variant	0	2 (1.4)	2 (0.7)
Midcavity obstruction without apical aneurysm	12 (8.5)	15 (10.7)	27 (9.6)
Midcavity obstruction with apical aneurysm	1 (0.7)	1 (0.7)	2 (0.7)
Concentric	18 (12.7)	14 (10.0)	32 (11.3)
Other	11 (7.7)	11 (7.9)	22 (7.8)
Time since initial HCM diagnosis (years)			
Mean (SD)	5.55 (5.415)	6.02 (6.474)	5.79 (5.958)
Median	4.08	4.06	4.07
Min, Max	0.0, 26.1	0.0, 45.9	0.0, 45.9
Any select cardiovascular medical history, n (%)[a]	47 (33.1)	46 (32.9)	93 (33.0)
Cardiac disorders	38 (26.8)	34 (24.3)	72 (25.5)
Paroxysmal atrial fibrillation	21 (14.8)	20 (14.3)	41 (14.5)
Coronary artery disease	19 (13.4)	16 (11.4)	35 (12.4)
Sustained ventricular tachycardia	2 (1.4)	2 (1.4)	4 (1.4)
Permanent atrial fibrillation	2 (1.4)	1 (0.7)	3 (1.1)
Ventricular fibrillation	1 (0.7)	2 (1.4)	3 (1.1)
Myocardial infarction	1 (0.7)	1 (0.7)	2 (0.7)
Nervous system disorders	15 (10.6)	17 (12.1)	32 (11.3)
Cardiac syncope	15 (10.6)	17 (12.1)	32 (11.3)
Any cardiovascular procedure history, n (%)	30 (21.1)	23 (16.4)	53 (18.8)
Implantable cardioverter defibrillator insertion	22 (15.5)	17 (12.1)	39 (13.8)
Percutaneous coronary intervention	6 (4.2)	5 (3.6)	11 (3.9)
Cardiac pacemaker insertion	5 (3.5)	4 (2.9)	9 (3.2)

HCM = hypertrophic cardiomyopathy; LV = left ventricular; Max = maximum; MedDRA = Medical Dictionary for Regulatory Activities; Min = minimum; SD = standard deviation

a Only data collected on the Cardiovascular Medical History electronic case report form (eCRF) were included in this summary. Reported terms were prespecified in the eCRF. MedDRA version 26.0 was used for coding medical history.

Table 29. Other General Medical History Reported for > 10% of Participants Overall

Preferred Term	Aficamten (N=142) n (%)	Placebo (N=140) n (%)	Overall (N=282) n (%)
Hypertension[a]	68 (47.9)	64 (45.7)	132 (46.8)
Hyperlipidaemia	45 (31.7)	31 (22.1)	76 (27.0)
Gastrooesophageal reflux disease	20 (14.1)	17 (12.1)	37 (13.1)
Hypercholesterolaemia	20 (14.1)	16 (11.4)	36 (12.8)
Dyslipidaemia	16 (11.3)	17 (12.1)	33 (11.7)

Note: MedDRA version 26.0 was used for coding medical history.
[a] An additional 13 participants overall (7 in the aficamten group and 6 in the placebo group) reported essential hypertension.

Concomitant medications

Background medications for HCM used at baseline are summarized in Table 32. Overall, beta-blockers were used by 61.3% of participants (60.6% aficamten, 62.1% placebo); and non-dihydropyradine calcium channel blockers were used by 28.7% of participants (31.7% aficamten, 25.7% placebo). In addition, 12.8% of participants (11.3% aficamten, 14.3% placebo) were taking disopyramide. Overall, 14.5% of participants (13.4% aficamten, 15.7% placebo) were not taking any background medication for HCM at baseline.

Table 30. Baseline Use of Background Medications for HCM

	Aficamten (N=142) n (%)	Placebo (N=140) n (%)	Overall (N=282) n (%)
Use of beta-blockers at randomization	86 (60.6)	87 (62.1)	173 (61.3)
Beta-blockers used by > 10% of participants overall			
Metoprolol succinate	28 (19.7)	25 (17.9)	53 (18.8)
Bisoprolol	21 (14.8)	24 (17.1)	45 (16.0)
Use of non-dihydropyradine calcium channel blockers	45 (31.7)	36 (25.7)	81 (28.7)
Non-dihydropyradine calcium channel blockers used by > 10% of participants overall			
Verapamil	19 (13.4)	13 (9.3)	32 (11.3)
Diltiazem	16 (11.3)	13 (9.3)	29 (10.3)
Use of disopyramide	16 (11.3)	20 (14.3)	36 (12.8)
No use of background medication	19 (13.4)	22 (15.7)	41 (14.5)

This table presents typical background medications for hypertrophic cardiomyopathy.
Baseline medications were defined as medications that started before the first dose of IP and ended after the first dose of IP or were ongoing. WHO Drug Global Version March 2023 was used to code the medications.

- **Numbers analysed**

All analyses were performed on the full analyses set, with imputations performed for missing data under the missing at random assumption. For the primary endpoint, at Week 24, 9 participants (6.3%) in the aficamten group and 10 participants (7.1%) in the placebo group had missing pVO2 data. An overview of missing data is on the primary endpoint is shown in Table 33. The number of missing data for secondary endpoints were lower than for pVO2 and balanced between arms.

Table 31. Summary of Missing pVO2 on CPET at Week 24

	Aficamten (N=142)	Placebo (N=140)	Overall (N=282)
Missing Week 24 pVO_2	9 (6.3)	10 (7.1)	19 (6.7)
Early Termination from Study	3 (2.1)	3 (2.1)	6 (2.1)
Study Terminated by Sponsor	0	0	0
Physician Decision	0	2 (1.4)	2 (0.7)
Adverse Event	0	1 (0.7)	1 (0.4)
Lost to Follow-up	0	0	0
Withdrawal by Subject	2 (1.4)	0	2 (0.7)
Death	0	0	0
Protocol Deviation	0	0	0
Other	1 (0.7)	0	1 (0.4)
Invalid pVO_2	6 (4.2)	7 (5.0)	13 (4.6)
CPET MOP	2 (1.4)	1 (0.7)	3 (1.1)
Technical	4 (2.8)	6 (4.3)	10 (3.5)
Transient	0	0	0

CPET = cardiopulmonary exercise testing; MOP = Manual of Operating Procedures; pVO_2 = peak oxygen uptake
Notes: Reason for participants early termination from the study are presented. These participants terminated early from treatment due to the same reasons, with exception of one participant from the placebo group who terminated early from the study due to physician's decision to end treatment due to an adverse event and one participant from the aficamten group who terminated early from the study due to reason of other and ended treatment due to protocol deviation.

- **Outcomes and estimation**

Primary Endpoint: Change in pVO2 by CPET from Baseline to Week 24 (Primary Estimand)

The LS mean change in pVO2 by CPET from baseline to Week 24 was statistically significantly greater in the aficamten group than in the placebo group: 1.76 mL/kg/min vs 0.02 mL/kg/min (Table 34). The LS mean difference between treatment groups was 1.74 mL/kg/min (95% CI: 1.04, 2.44; p < 0.0001).

Table 32. Change in pVO2 on CPET from Baseline to Week 24 (Multiple Imputation)

pVO_2 (mL/kg/min)	Aficamten (N=142)	Placebo (N=140)
Baseline		
n	142	140
Mean (SD)	18.38 (4.450)	18.59 (4.505)
Q1, Q3	14.90, 21.10	15.18, 21.21
Week 24		
n	133	130
Mean (SD)	20.21 (5.209)	18.58 (4.716)
Q1, Q3	16.60, 23.70	15.30, 21.90
Change from Baseline - Week 24		
n	133	130
Mean (SD)	1.78 (3.122)	0.01 (2.729)
Q1, Q3	−0.32, 3.22	−1.70, 1.55
LS Mean (SE)	1.76 (0.254)	0.02 (0.253)
LS Mean 95% CI	(1.26, 2.26)	(−0.48, 0.52)
LS Mean Diff vs. Placebo (SE)	1.74 (0.355)	
LS Mean Diff vs. Placebo 95% CI	(1.04, 2.44)	
p-value	< 0.0001	

ANCOVA = analysis of covariance; CI = confidence interval; CPET = cardiopulmonary exercise testing; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LS = least squares; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; pVO_2 = peak oxygen uptake; Q1, Q3 = first and third quartiles; SD = standard deviation; SE = standard error
Notes: Missing data were imputed using regression multiple imputation including treatment group, randomization stratification factors, baseline pVO_2, sex, age, baseline hemoglobin, baseline body weight, baseline KCCQ CSS, baseline NYHA class, and the last available post randomization NYHA functional class, resting and Valsalva LVOT under missing at random assumption.
Each completed dataset was analyzed using ANCOVA model with fixed effects of treatment, beta blocker use (Yes/No), CPET modality and baseline pVO_2 and baseline body weight as covariates. Results from all 100 imputed datasets were combined for overall inference using Rubin's rules.

Sensitivity Analysis: Placebo-based Imputation

At Week 24, 9 participants (6.3%) in the aficamten group and 10 participants (7.1%) in the placebo group had missing pVO2 data. The missing data were attributed to either early termination from the study or invalid pVO2 measures assessed by the CPET core laboratory at Week 24.

The results of this sensitivity analysis were consistent with the primary analysis and showed that the LS mean change from baseline in pVO2 at Week 24 was 1.69 mL/kg/min for the aficamten group compared with 0.00 mL/kg/min for the placebo group. The LS mean difference between treatment groups was 1.69 mL/kg/min (95% CI: 0.99, 2.39; p < 0.0001) and was statistically significant, consistent with the results of the primary analysis.

Sensitivity Analysis: Tipping Point

For the tipping point analysis, imputed pVO2 values (obtained from the multiple imputation model and used for the primary analysis) for participants who had missing data in the aficamten group were successively shifted lower (ie, 90% of the imputed value down to 25% of the imputed value) to determine at what point the treatment effect was no longer statistically significant. For this analysis, imputed values in the placebo group were not shifted. The results of this analysis showed that the p-value remained < 0.01 through a shift to 50% of the imputed values; and it remained < 0.05 through a shift to 30% of the imputed values, see Table 35.

Table 33. Tipping Point Analysis: Change in pVO2 on CPET from Baseline at Week 24 (Full Analysis Set)

Tipping Point Shift Scale	LS Mean (SE)		LS Mean Difference vs Placebo (95% CI)	p-value
	Aficamten (N=142)	Placebo (N=140)		
100% (Primary Analysis)	1.76 (0.254)	0.02 (0.253)	1.74 (1.04, 2.44)	< 0.0001
90%	1.63 (0.253)	0.02 (0.254)	1.62 (0.92, 2.32)	< 0.0001
80%	1.51 (0.256)	0.02 (0.259)	1.49 (0.78, 2.20)	< 0.0001
70%	1.39 (0.263)	0.01 (0.267)	1.37 (0.65, 2.10)	< 0.001
60%	1.26 (0.273)	0.01 (0.279)	1.24 (0.49, 2.00)	0.001
50%	1.14 (0.285)	0.01 (0.292)	1.12 (0.34, 1.91)	0.005
40%	1.02 (0.298)	0.00 (0.305)	1.02 (0.19, 1.85)	0.016
30%	0.91 (0.313)	0.01 (0.321)	0.91 (0.04, 1.78)	0.041
25%	0.88 (0.319)	0.01 (0.326)	0.87 (−0.02, 1.75)	0.055

CI = confidence interval; CPET = cardiopulmonary exercise testing; LS = least squares; pVO_2 = peak oxygen uptake; SE = standard error
Notes: Missing data were imputed using the same imputation model for the primary estimand applying ranges of scale shift (scale = 100% as no adjustment is made) to the values imputed for the aficamten group.
The model used to analyze this data was the same as that used for the primary estimand.

Sensitivity Analysis: COVID-19 impact.

The potential impact of COVID-19 on the primary endpoint was assessed. The results of this analysis showed little difference from the primary analysis: the LS mean change from baseline in pVO2 at Week 24 was 1.76 mL/kg/min for the aficamten group and 0.04 mL/kg/min for the placebo group. The treatment difference vs placebo was 1.72 mL/kg/min and statistically significant (95% CI: 1.02, 2.42; p < 0.0001)

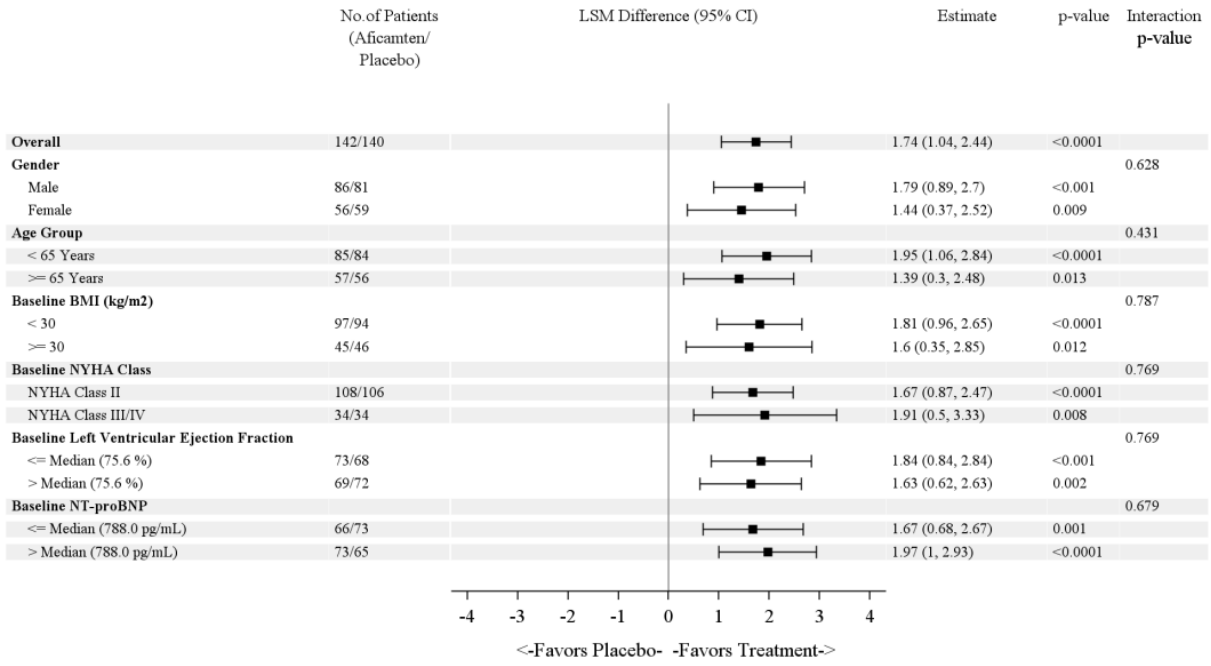
Sensitivity analysis: MMRM

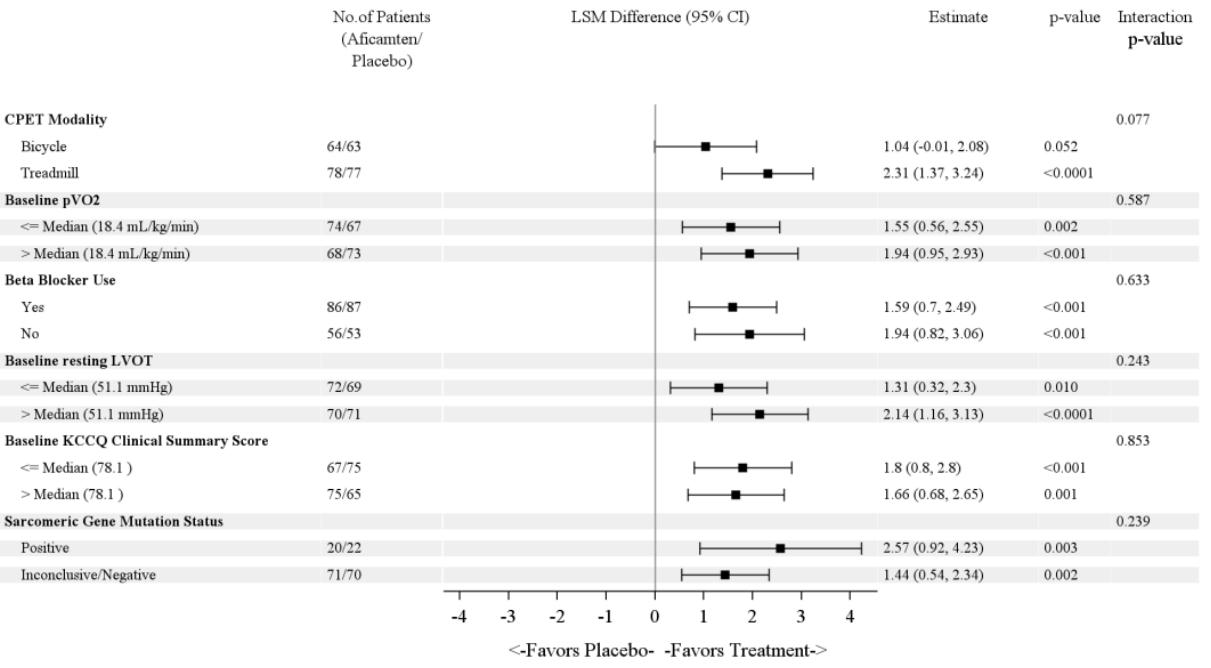
Another sensitivity analysis is to fit a repeated measures mixed model to pVO2 baseline and Week 24 data. The results of the analysis were consistent with the primary analysis: the LS mean change from baseline in pVO2 at Week 24 was 1.75 mL/kg/min for the aficamten group and 0.03 mL/kg/min for the placebo group. The treatment difference vs placebo was 1.72 mL/kg/min and statistically significant (95% CI: 1.02, 2.42; p < 0.0001).

Subgroup analyses of the primary endpoint

Subgroup analyses are presented in a forest plot in Figure 15. Results across all subgroups were consistent with results from the primary analysis, with participants in the aficamten group showing greater change from baseline at Week 24 in pVO2 than participants in the placebo group, with no apparent interaction. Predefined subgroups included sex, age, baseline BMI, baseline NYHA class, baseline LVEF, baseline NT-proBNP, CPET modality, baseline pVO2, baseline beta-blocker use, baseline resting LVOT, baseline KCCQ-CSS, and sarcomeric gene mutation status. Analysis of participants at sites submitted to the US IND (IND sites; 49 participants in the aficamten group and 45 in the placebo group) versus sites not submitted to the US IND (non-IND sites; 93 participants in the aficamten group and 95 in the placebo group) showed that the change from baseline at Week 24 in pVO2 on CPET was statistically significantly greater with aficamten than placebo treatment at both IND and non-IND sites ($p = 0.016$ and < 0.0001 respectively), with no treatment interaction ($p = 0.566$).

Analysis of the primary endpoint among participants who were SRT eligible at baseline (32 aficamten, 29 placebo) showed a statistically significantly greater change from baseline in pVO2 on CPET in the aficamten group compared with the placebo group (with an LS mean difference vs placebo of 2.09 mL/kg/min [95% CI: 0.85, 3.33; $p = 0.001$]).





ANCOVA = analysis of covariance; BMI = body mass index; CPET = cardiopulmonary exercise testing; KCCQ = Kansas City Cardiomyopathy Questionnaire; LSM = least squares mean; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pVO_2 = peak oxygen uptake
Notes: The same imputed data for the primary estimand are used for the subgroup analysis. Each completed dataset was analyzed by including the subgroup effect and subgroup by treatment interaction term to the primary ANCOVA model. Results from all 100 imputed datasets are combined for overall inference.

Figure 15. Forest Plot of Change from Baseline to Week 24 in pVO2 on CPET by Subgroups (Multiple Imputation)

The Applicant has also performed a requested post-hoc subgroup analyses according to a history of atrial fibrillations. The least squares (LS) mean improvement in pVO2 with aficamten compared to placebo for patients with a history of atrial fibrillation/flutter (N = 44) versus patients without a history of atrial fibrillation/flutter (N = 238) at Week 24 is 1.61 mL/kg/min (95% CI: -0.2; 3.42; p = 0.081) and 1.76 mL/kg/min (95% CI: 1.00, 2.52; p < 0.0001), respectively.

The Applicant has also performed the requested post-hoc subgroup analysis according to EU and non-EU region. The LS mean improvement in pVO_2 with aficamten compared to placebo for patients from the EU is 1.70 mL/min/kg (N = 115; 95%CI: 0.60, 2.79; p = 0.003) and 1.73 mL/min/kg (N = 167; 95% CI: 0.82, 2.65; p < 0.001) in patients from the rest of the world (United States [US], China, and Israel).

The Applicant has also performed the requested post-hoc subgroup analysis according to disopyramide and calcium antagonist use. The LS mean improvement in pVO_2 with aficamten compared to placebo for patients using disopyramide is 2.47 mL/min/kg (N = 32; 95%CI: 0.44, 4.50; p = 0.017) and 1.62 mL/min/kg (N = 231; 95% CI: 0.87, 2.37; p < 0.001) in patients not using disopyramide. The LS mean improvement in pVO_2 with aficamten compared to placebo for patients using calcium antagonists is 2.05 mL/min/kg (N = 79; 95%CI: 0.77, 3.33; p = 0.002) and 1.68 mL/min/kg (N = 184; 95% CI: 0.85, 2.51; p < 0.001) in patients not using calcium antagonists.

The Applicant also included a planned subgroup analyses according to results of mutation analyses conducted by a genetics core laboratory. The data resulting from the genetic testing substudy based on DNA sample collection during the study in consenting participants (n = 184 out of 282 participants) and reflects the results of mutation analyses conducted by a genetics core laboratory. The LS mean improvement in pVO_2 with aficamten compared to placebo for patients with core-laboratory sarcomeric mutation is 2.57 mL/min/kg (N = 41; 95%CI: 0.92, 4.23; p = 0.003) and 1.45 mL/min/kg (N = 135; 95% CI: 0.55, 2.35; p = 0.002) in patients without.

Post-hoc justification of the clinical relevance:

Further, the Applicant conducted additional analyses in CY 6031 to validate the clinical relevance of the magnitude of a 1.7 mL/kg/min increase in pVO2 with aficamten compared with placebo as measured by NYHA Functional Class and patient reported outcomes. Change in pVO2 was compared with clinically relevant anchors of NYHA Functional Class change, Patient Global Impression of Change (PGI C), and Kansas City Cardiomyopathy Questionnaire-Physical Limitation Scale (KCCQ PLS) score by the empirical cumulative distribution function (eCDF), respectively. The eCDF curves (Figure 16, Figure 17 and Figure 18) show separation of pVO2 by categories of change in NYHA Functional Class, PGI-C, and KCCQ-PLS with incrementally larger increases of pVO2 associated with categorical improvements of each anchor. For NYHA Functional Class, 1 and 2 class improvements were associated with median pVO2 increases of 1.1 and 1.6 mL/kg/min. For PGI-C, minimally improved and very much improved were associated with median pVO2 increases of 0.8 and 2.0 mL/kg/min. For KCCQ-PLS, a small improvement and very large improvement were associated with median pVO2 increases of 0.3 and 1.6 mL/kg/min.

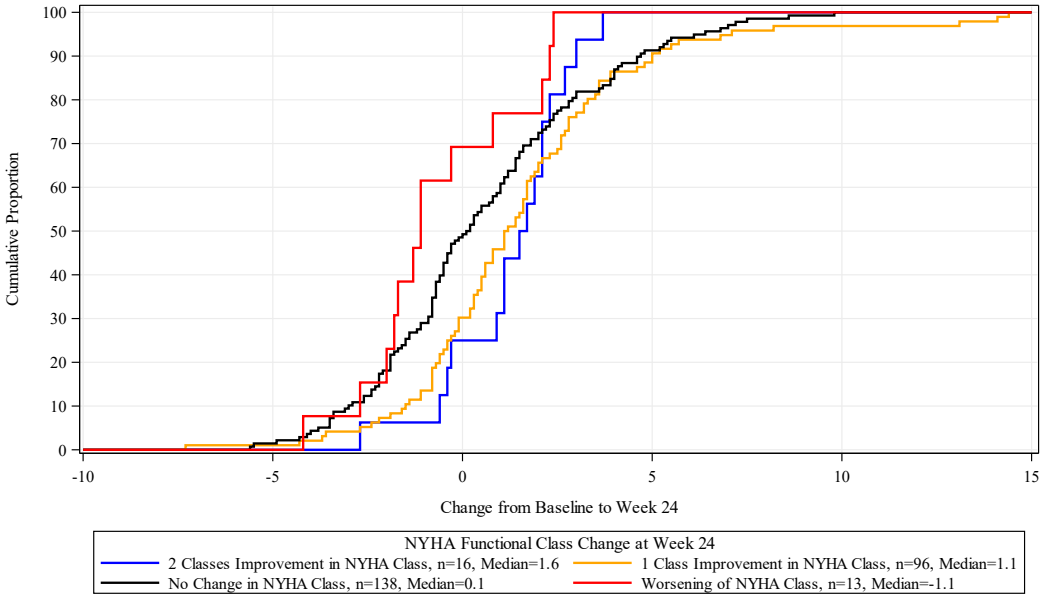


Figure 16. Cumulative Distribution of Change from Baseline to Week 24 in pVO2 by NYHA Functional Class Change

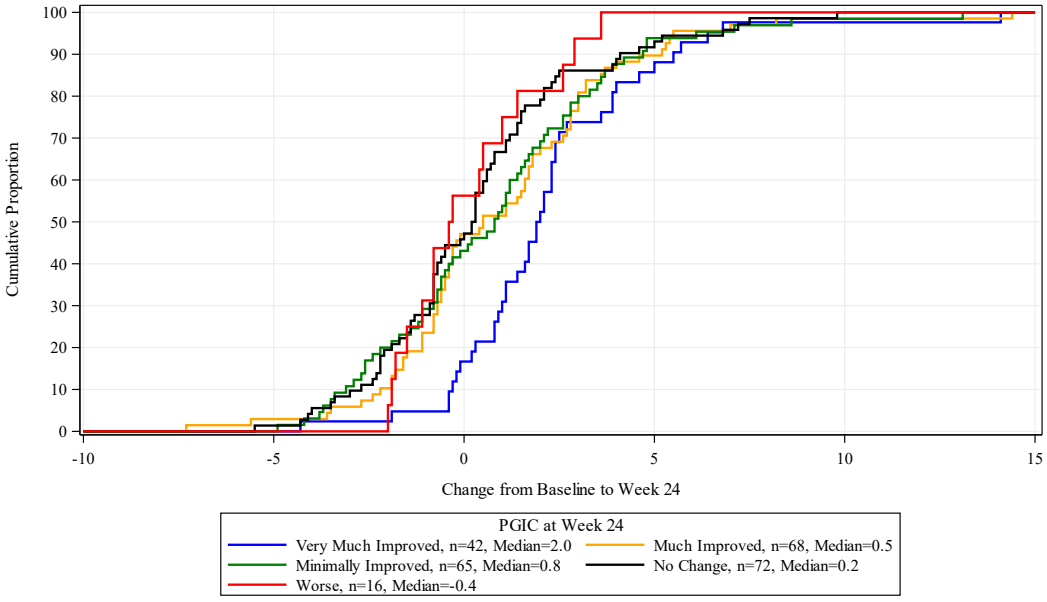


Figure 17. Cumulative Distribution of Change from Baseline to Week 24 in pVO2 by PGI C

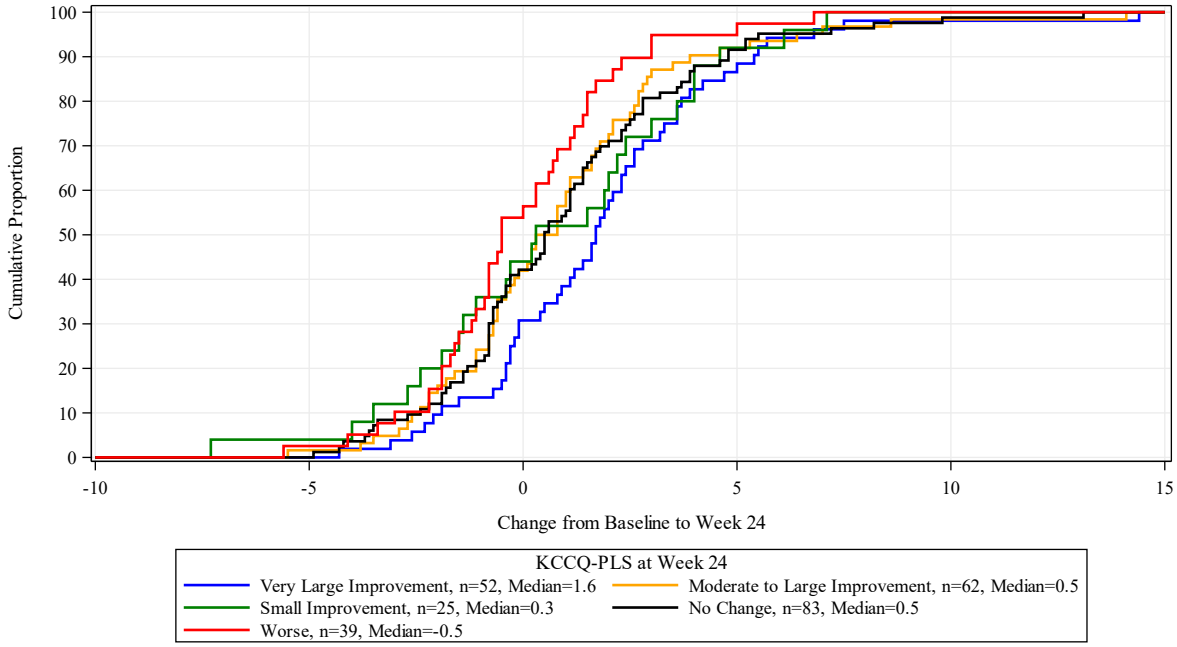


Figure 18. Cumulative Distribution of Change from Baseline to Week 24 in pVO2 by KCCQ PLS

Secondary and exploratory endpoints:

An overview of the results of the secondary endpoint is shown in Table 36. This table demonstrated that all of the prespecified secondary endpoint, in hierarchical order, were statistically significant. These analyses demonstrate a significant improvement in KCCQ-CSS, NYHA functional class improvement, reductions in Valsalva LVOT-G, lower duration SRT eligible and an increase in total workload during CPET.

1. Table 34. Overview of Secondary Endpoint Results (Full Analysis Set)

Endpoint	Aficamten[a] (N=142)	Placebo[a] (N=140)	Difference[a] (95% CI)	p-value
Week 24				
Change in KCCQ-CSS[b]	11.6 (1.01)	4.3 (1.00)	7.3 (4.6, 10.1)	< 0.0001
Proportion of Participants with ≥ 1 NYHA Class Improvement[c]	83 (58.5)	34 (24.3)	OR[d]: 4.408 (2.560, 7.598) Diff[a]: 34.2 (23.4, 45.0)	< 0.0001
Change in Valsalva LVOT-G[e] (mmHg)	−48 (2.4)	2 (2.4)	−50 (−57, −44)	< 0.0001
Proportion of Participants with Valsalva LVOT-G < 30 mmHg	70 (49.3)	5 (3.6)	OR[d]: 25.479 (10.107, 88.198) Diff[a]: 45.7 (36.9, 54.5)	< 0.0001
Duration of SRT eligibility[f] (days)	35.3 (7.89)	113.4 (8.05)	−78.1 (−99.8, −56.3)	< 0.0001
Week 12				
Change in KCCQ-CSS[b]	11.1 (0.92)	4.0 (0.91)	7.0 (4.5, 9.5)	< 0.0001
Proportion of Participants with ≥ 1 NYHA Class Improvement[c]	69 (48.6)	25 (17.9)	OR[d]: 4.604 (2.559, 8.445) Diff[a]: 30.8 (20.6, 41.0)	< 0.0001
Change in Valsalva LVOT-G[e] (mmHg)	−46 (2.4)	3 (2.4)	−48 (−55, −42)	< 0.0001
Proportion of Participants with Valsalva LVOT-G < 30 mmHg	74 (52.1)	8 (5.7)	OR[d]: 18.041 (7.842, 44.400) Diff[a]: 46.4 (37.3, 55.5)	< 0.0001
Week 24				
Change in Total Workload during CPET[g] (Watts)	13.4 (2.12)	1.2 (2.14)	12.2 (6.4, 18.0)	< 0.0001

ANCOVA = analysis of covariance; CI = confidence interval; CPET = cardiopulmonary exercise testing; Diff = difference; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LS = least squares; LVOT-G = left ventricular outflow tract gradient; MMRM = mixed model for repeated measures; NYHA = New York Heart Association; OR = odds ratio; SE = standard error; SRT = septal reduction therapy

[a] Note: LS means (SE) and LS mean difference (95% CI) are presented for continuous endpoints. The number (percentage) of responders and rate difference are presented for binary endpoints.

[b] Analyzed using an MMRM with baseline as covariate, randomization stratification factors, visit, treatment group, region, and interaction terms of treatment by visit, baseline by visit, region by treatment, region by visit, baseline by region, treatment by visit and region, baseline by visit and region as fixed effects

[c] Analyzed using Cochran–Mantel–Haenszel test stratified by beta blocker use (Yes/No) and CPET modality

[d] Common odds ratio (exact 95% CI of the odds ratio)

[e] Analyzed using an MMRM with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit

[f] Analyzed using an ANCOVA model includes treatment and randomization stratification factor beta blocker use/non-use as fixed effects and significant baseline characteristics as covariates.

[g] Analyzed using multiple imputation, with each completed data set analyzed using ANCOVA, then all data sets combined for overall inference using Rubin's rules.

From a regulatory perspective, the exploratory endpoints participants remaining eligible for SRT and responder analyses on KCCQ are considered important, even though not prespecified as secondary analyses and are therefore presented in detail below.

SRT eligibility

At baseline, 32 participants in the aficamten group and 29 participants in the placebo group were SRT eligible. Baseline characteristics were generally similar across the SRT eligible patients in the aficamten and placebo group, including age (62 vs 62 years), bmi (28.9 vs 29.0 kg/m^2), resting LVOT-G (65 vs 69 mmHg), post-valsalva LVOT-G (94 vs 95 mmHg), LVEF (74.2% vs 74.5%) and NT-proBNP (918 vs 742 pg/mL).

Of these participants 4 (12.5%) in the aficamten group and 14 (48.3%) in the placebo group remained SRT eligible at Week 24. The common rate difference between the treatment groups was −36.5 (95%

CI: −58.5, −14.5; p = 0.002), and the common odds ratio (vs placebo) was 0.163 (95% CI: 0.031, 0.614; p = 0.005).

The robustness of this endpoint is supported by duration spend eligible, where aficamten treatment resulted in a significant reduction in the time spent SRT eligible by an LS mean of −78.1 days (95% CI: −99.8, −56.3; p < 0.0001) compared with placebo. Furthermore, the aforementioned effect on SRT eligibility was not solely driven by one of the components (LVOT-G and NYHA) as aficamten had both an effect on LVOT-G (treatment difference vs placebo was −48 mmHg (95% CI: −55, −42; p < 0.0001)) and NYHA functional class improvement (odds ratio vs placebo for ≥ 1 improvement in NYHA class was 4.41 (95% CI: 2.56, 7.60; p < 0.0001)).

The Applicant has provided a listing of participants who were not SRT eligible at baseline but became SRT eligible during 24 weeks of study treatment during CY 6031. A total of 23 participants (3 aficamten; 20 placebo) became SRT eligible at any time during the study.

KCCQ-CSS

At week 24, 69 (48.6%) of the aficamten treated patients and 38 (27.1%) of the placebo treated patients had an improvement of ≥ 10 points in the KCCQ-CSS. The common odds ratio vs placebo for an improvement of ≥ 10 points in the KCCQ-CSS was 2.58 (1.52; 4.40); p < 0.001 in favor of aficamten. Using alternative cut-offs (5, 15, 20), comparable effects were found, see Table 37. The robustness of these findings is supported by LS mean change in KCCQ-CSS and total KCCQ score. The LS mean change in KCCQ-CSS from baseline to Week 24 was 11.6 points in the aficamten group and 4.3 points in the placebo group. The LS mean difference between treatment groups in in KCCQ-CSS of 7.3 points was statistically significant, favoring aficamten (95% CI: 4.6, 10.1; p < 0.0001). A comparable results was found for the total score, where the LS mean difference vs placebo was 8.0 (95% CI: 4.9; 11.2) points increase in total KCCQ score (P<0.0001).

2. Table 35. Proportion of Participants with Improvement of ⩾ 5, 10, 15, or 20 Points in KCCQ-CSS at Weeks 12 and 24

KCCQ-CSS Improvement	Aficamten (N=142) n (%)	Placebo (N=140) n (%)	Rate Difference (95% CI) p-value	Common Odds Ratio (95% CI) p-value
Week 12				
≥ 5 Points	90 (63.4)	70 (50.0)	13.5 (2.1, 24.8) p = 0.022	1.758 (1.055, 2.921) p = 0.029
≥ 10 Points	63 (44.4)	33 (23.6)	20.8 (10.0, 31.6) p < 0.001	2.586 (1.506, 4.470) p < 0.001
≥ 15 Points	42 (29.6)	19 (13.6)	16.1 (6.6, 25.5) p < 0.001	2.686 (1.431, 5.313) p = 0.001
≥ 20 Points	34 (23.9)	11 (7.9)	16.1 (7.9, 24.4) p < 0.001	3.766 (1.751, 8.748) p < 0.001
Week 24				
≥ 5 Points	87 (61.3)	70 (50.0)	11.3 (−0.1, 22.8) p = 0.054	1.597 (0.964, 2.640) p = 0.071
≥ 10 Points	69 (48.6)	38 (27.1)	21.5 (10.6, 32.5) p < 0.001	2.580 (1.517, 4.396) p < 0.001
≥ 15 Points	42 (29.6)	19 (13.6)	16.1 (6.7, 25.4) p = 0.001	2.733 (1.428, 5.288) p = 0.002
≥ 20 Points	31 (21.8)	11 (7.9)	14.0 (6.0, 22.1) p < 0.001	3.359 (1.524, 7.662) p = 0.001

CI = confidence interval; CPET = cardiopulmonary exercise testing; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score
Notes: Proportion of responders was analyzed using the Cochran– Mantel–Haenszel test stratified by beta blocker use (Yes/No) and CPET modality. Participants with missing KCCQ-CSS were treated as non-responders in the analysis.

Cardiac biomarkers

The comparison at Week 24 showed that the aficamten group had an approximate 42% decrease in hs-cTnI whereas the placebo group showed minimal to no change ($p < 0.0001$). The comparison at Week 24 showed that the aficamten group had an approximate 80% decrease in NT-proBNP whereas the placebo group showed minimal to no change ($p < 0.0001$).

CMR substudy; effect on LV Mass, function, and structure by MRI

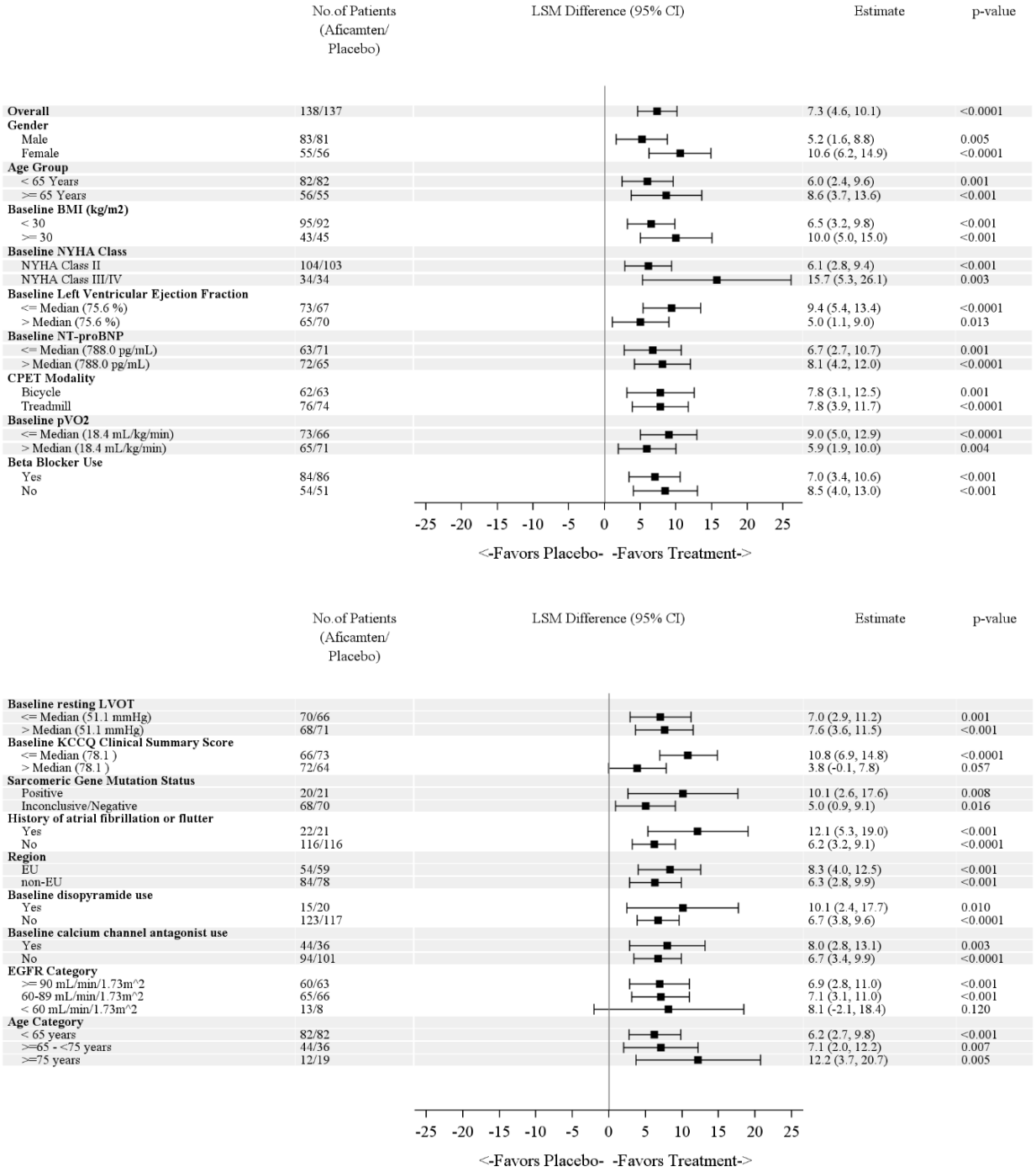
Fifty-seven of 282 participants (25 in the aficamten group and 32 in the placebo group) elected to participate in the CMR substudy. Of these participants, 50 (21 aficamten, 29 placebo) completed both baseline and Week 24 assessments. Changes in LV mass index, LVEF, LV septal wall thickness, LV lateral wall thickness, global LV wall thickness, LVESV, LVEDV, and LAVI are summarized in Table 38.

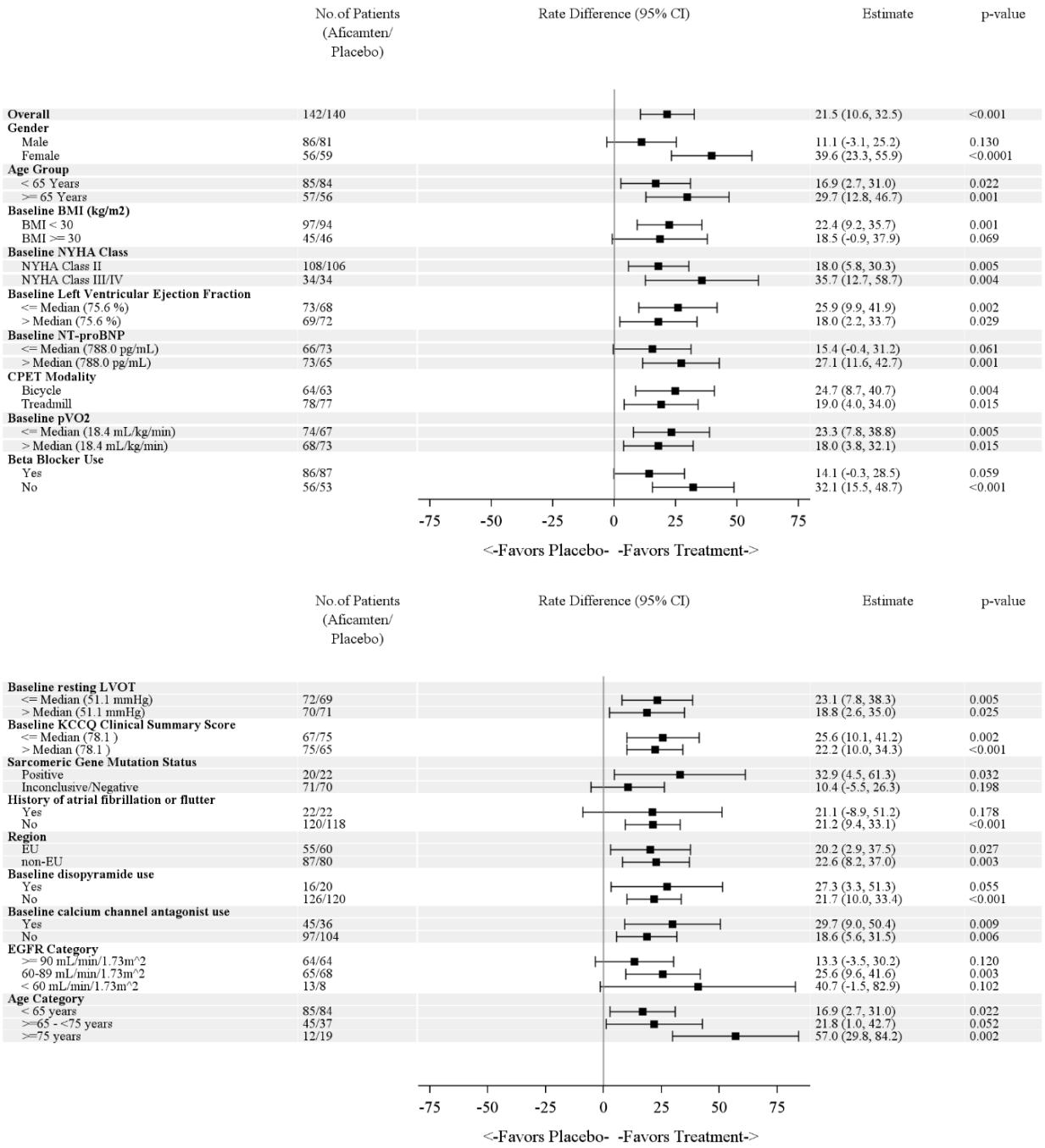
At Week 24, LV mass index, maximal LV septal wall thickness, maximal LV lateral wall thickness, and global LV max wall thickness all showed decreases from baseline in the aficamten group that were statistically significant compared to the changes observed in the placebo group (Table 37).

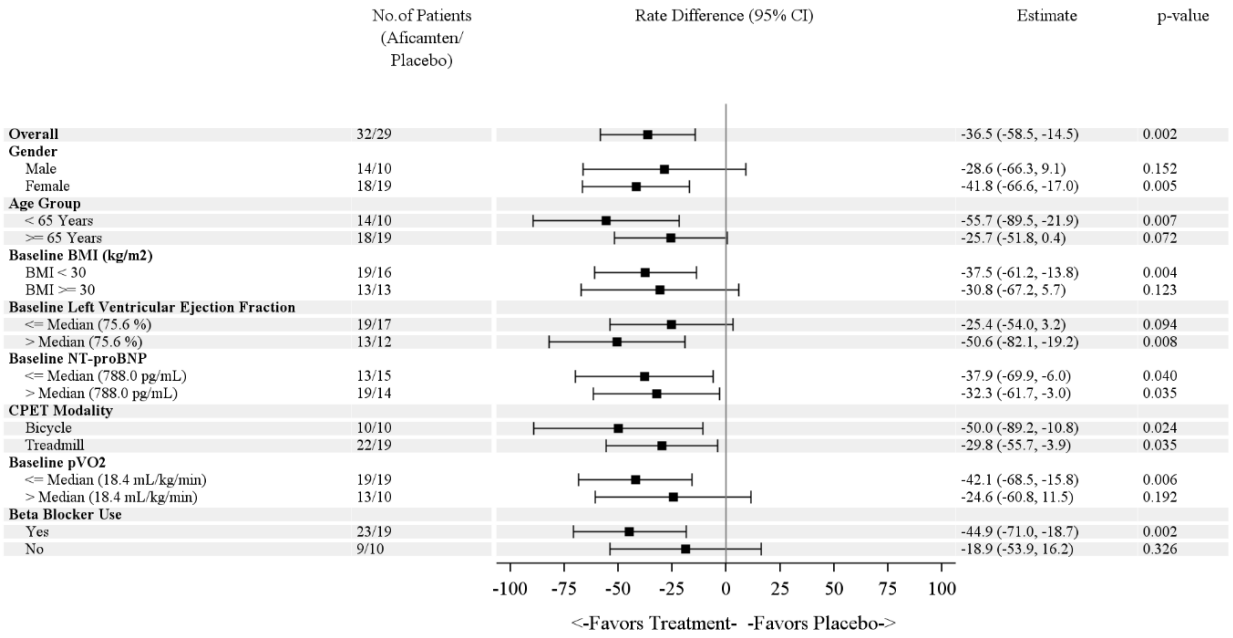
Table 36. Change from Baseline to Week 24 in CMR Parameters

CMR Parameter	Aficamten (N=25)	Placebo (N=32)	LS Mean Difference (95% CI)	p-value
LV mass index (g/m^2)				
Baseline				
n	25	32	—	—
Mean (SD)	113.9 (33.4)	109.4 (27.0)	—	—
Change from baseline to Week 24				
n	21	29	—	—
LS mean (SE)	−10.1 (3.6)	5.3 (2.9)	−15.4 (−24.5, −6.3)	0.001
LV septal wall thickness, maximal (mm)				
Baseline				
n	25	31	—	—
Mean (SD)	18.3 (4.0)	19.0 (3.9)	—	—
Change from baseline to Week 24				
n	21	27	—	—
LS mean (SE)	−1.6 (0.5)	0.2 (0.4)	−1.7 (−3.1, −0.4)	0.011
LV lateral wall thickness, maximal (mm)				
Baseline				
n	25	31	—	—
Mean (SD)	18.8 (4.0)	18.8 (4.5)	—	—
Change from baseline to Week 24				
n	21	27	—	—
LS mean (SE)	−1.6 (0.4)	0.1 (0.4)	−1.7 (−2.9, −0.6)	0.004
Global LV max wall thickness (mm)				
Baseline				
n	25	31	—	—
Mean (SD)	19.5 (4.0)	20.0 (4.2)	—	—
Change from baseline to Week 24				
n	21	28	—	—
LS mean (SE)	−1.6 (0.4)	0.5 (0.3)	−2.1 (−3.1, −1.1)	< 0.0001

Subgroup analyses of selected secondary endpoints are presented in Figure 19, Figure 20, Figure 21, Figure 22, Figure 21 and Figure 21, indicating general consistency of the treatment effects across prespecified subgroups.




No.of Patients (Aficamten/ Placebo)
Rate Difference (95% CI)
Estimate
p-value
Overall 142/140 21.5 (10.6, 32.5) <0.001
Gender
Male 86/81 11.1 (-3.1, 25.2) 0.130
Female 56/59 39.6 (23.3, 55.9) <0.0001
Age Group
< 65 Years 85/84 16.9 (2.7, 31.0) 0.022
>= 65 Years 57/56 29.7 (12.8, 46.7) 0.001
Baseline BMI (kg/m2)
BMI < 30 97/94 22.4 (9.2, 35.7) 0.001
BMI >= 30 45/46 18.5 (-0.9, 37.9) 0.069
Baseline NYHA Class
NYHA Class II 108/106 18.0 (5.8, 30.3) 0.005
NYHA Class III/IV 34/34 35.7 (12.7, 58.7) 0.004
Baseline Left Ventricular Ejection Fraction
<= Median (75.6 %) 73/68 25.9 (9.9, 41.9) 0.002
> Median (75.6 %) 69/72 18.0 (2.2, 33.7) 0.029
Baseline NT-proBNP
<= Median (788.0 pg/mL) 66/73 15.4 (-0.4, 31.2) 0.061
> Median (788.0 pg/mL) 73/65 27.1 (11.6, 42.7) 0.001
CPET Modality
Bicycle 64/63 24.7 (8.7, 40.7) 0.004
Treadmill 78/77 19.0 (4.0, 34.0) 0.015
Baseline pVO2
<= Median (18.4 mL/kg/min) 74/67 23.3 (7.8, 38.8) 0.005
> Median (18.4 mL/kg/min) 68/73 18.0 (3.8, 32.1) 0.015
Beta Blocker Use
Yes 86/87 14.1 (-0.3, 28.5) 0.059
No 56/53 32.1 (15.5, 48.7) <0.001
-75 -50 -25 0 25 50 75
<-Favors Placebo- -Favors Treatment->
No.of Patients (Aficamten/ Placebo)
Rate Difference (95% CI)
Estimate
p-value
Baseline resting LVOT
<= Median (51.1 mmHg) 72/69 23.1 (7.8, 38.3) 0.005
> Median (51.1 mmHg) 70/71 18.8 (2.6, 35.0) 0.025
Baseline KCCQ Clinical Summary Score
<= Median (78.1) 67/75 25.6 (10.1, 41.2) 0.002
> Median (78.1) 75/65 22.2 (10.0, 34.3) <0.001
Sarcomeric Gene Mutation Status
Positive 20/22 32.9 (4.5, 61.3) 0.032
Inconclusive/Negative 71/70 10.4 (-5.5, 26.3) 0.198
History of atrial fibrillation or flutter
Yes 22/22 21.1 (-8.9, 51.2) 0.178
No 120/118 21.2 (9.4, 33.1) <0.001
Region
EU 55/60 20.2 (2.9, 37.5) 0.027
non-EU 87/80 22.6 (8.2, 37.0) 0.003
Baseline disopyramide use
Yes 16/20 27.3 (3.3, 51.3) 0.055
No 126/120 21.7 (10.0, 33.4) <0.001
Baseline calcium channel antagonist use
Yes 45/36 29.7 (9.0, 50.4) 0.009
No 97/104 18.6 (5.6, 31.5) 0.006
EGFR Category
>= 90 mL/min/1.73m^2 64/64 13.3 (-3.5, 30.2) 0.120
60-89 mL/min/1.73m^2 65/68 25.6 (9.6, 41.6) 0.003
< 60 mL/min/1.73m^2 13/8 40.7 (-1.5, 82.9) 0.102
Age Category
< 65 years 85/84 16.9 (2.7, 31.0) 0.022
>=65 - <75 years 45/37 21.8 (1.0, 42.7) 0.052
>=75 years 12/19 57.0 (29.8, 84.2) 0.002
-75 -50 -25 0 25 50 75
<-Favors Placebo- -Favors Treatment->
Figure 20. Forest Plot: Proportion of Patients with ⩾ 10 points Improvement in KCCQ CSS at Week 24 by Subgroups



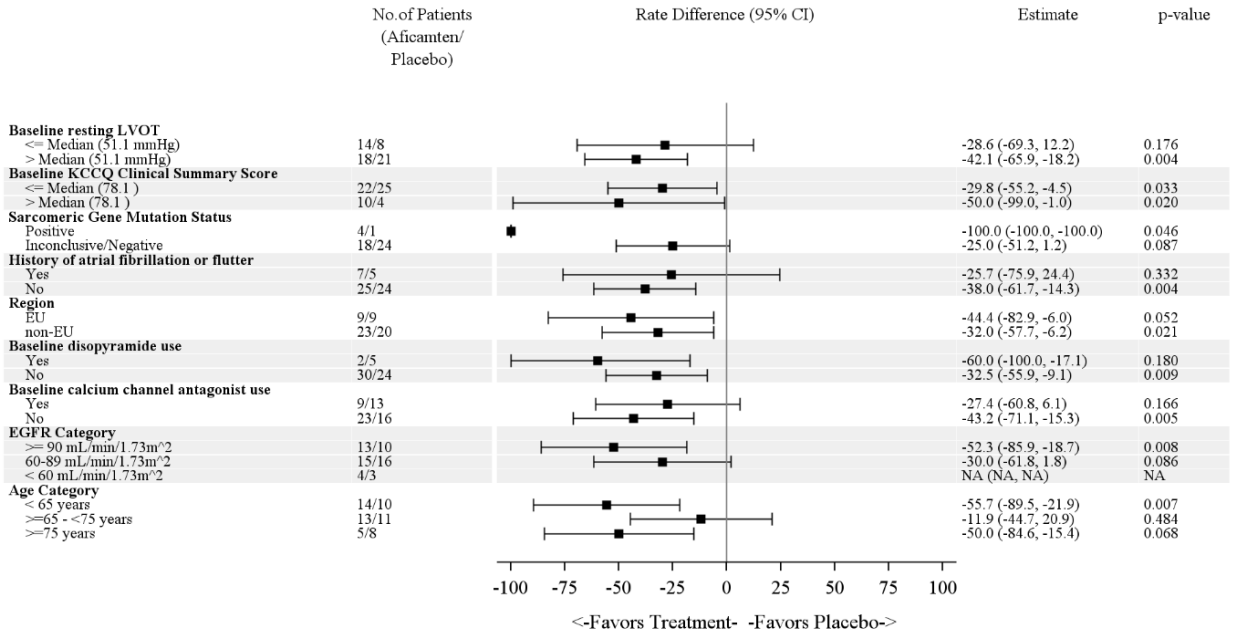
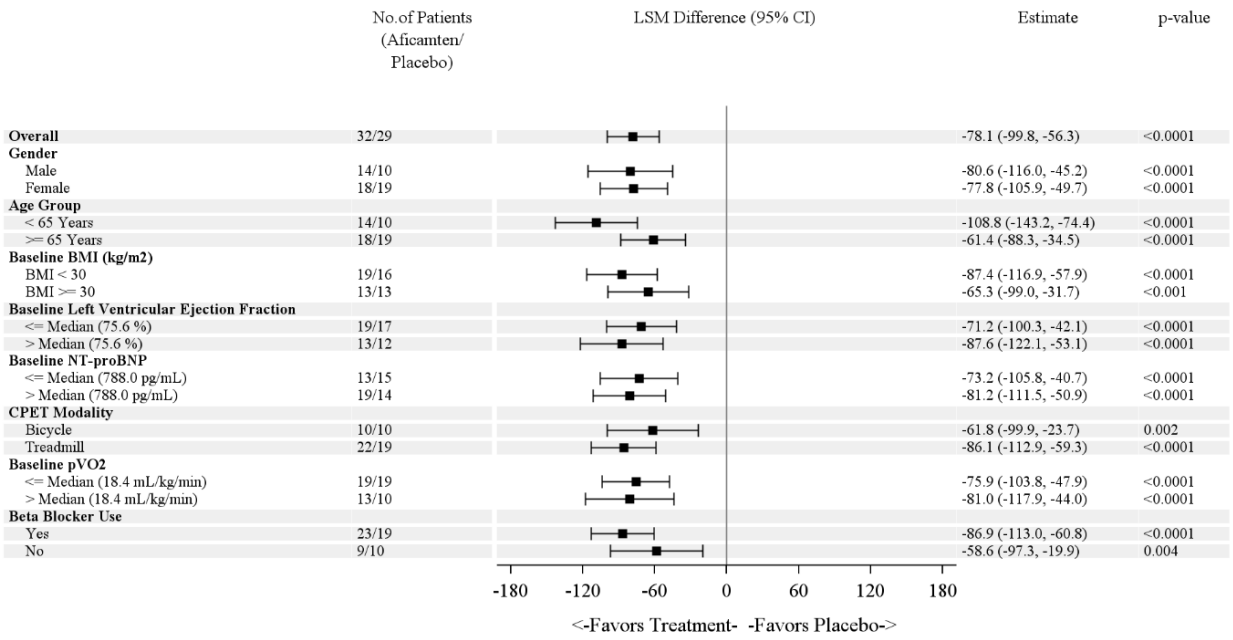
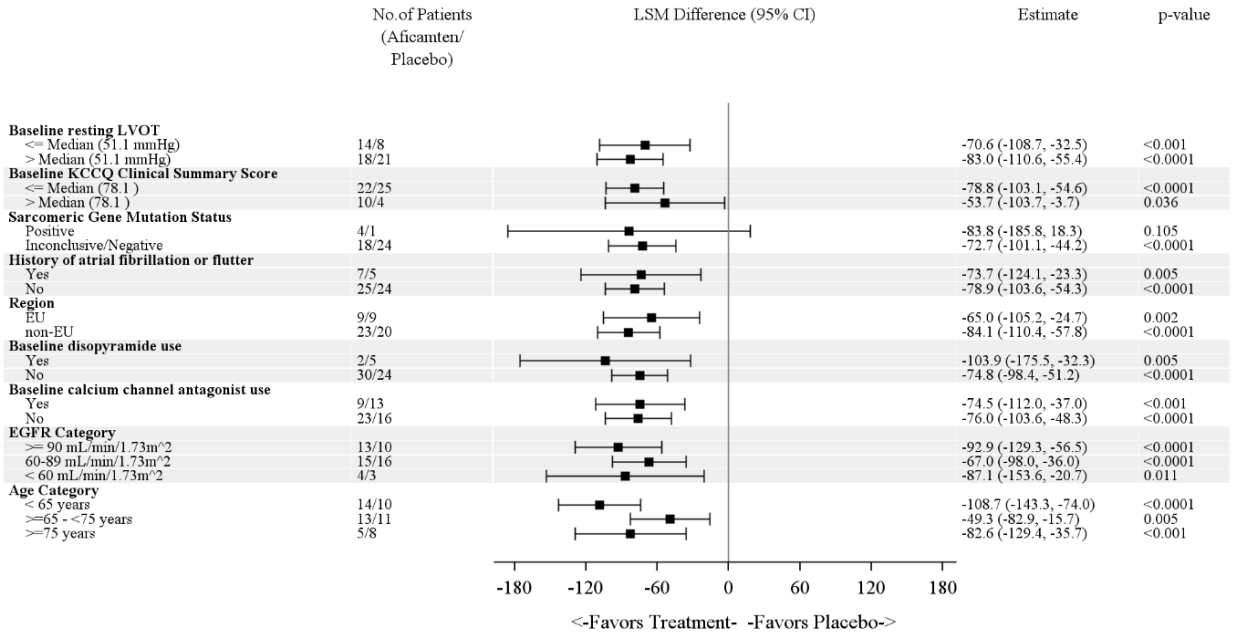
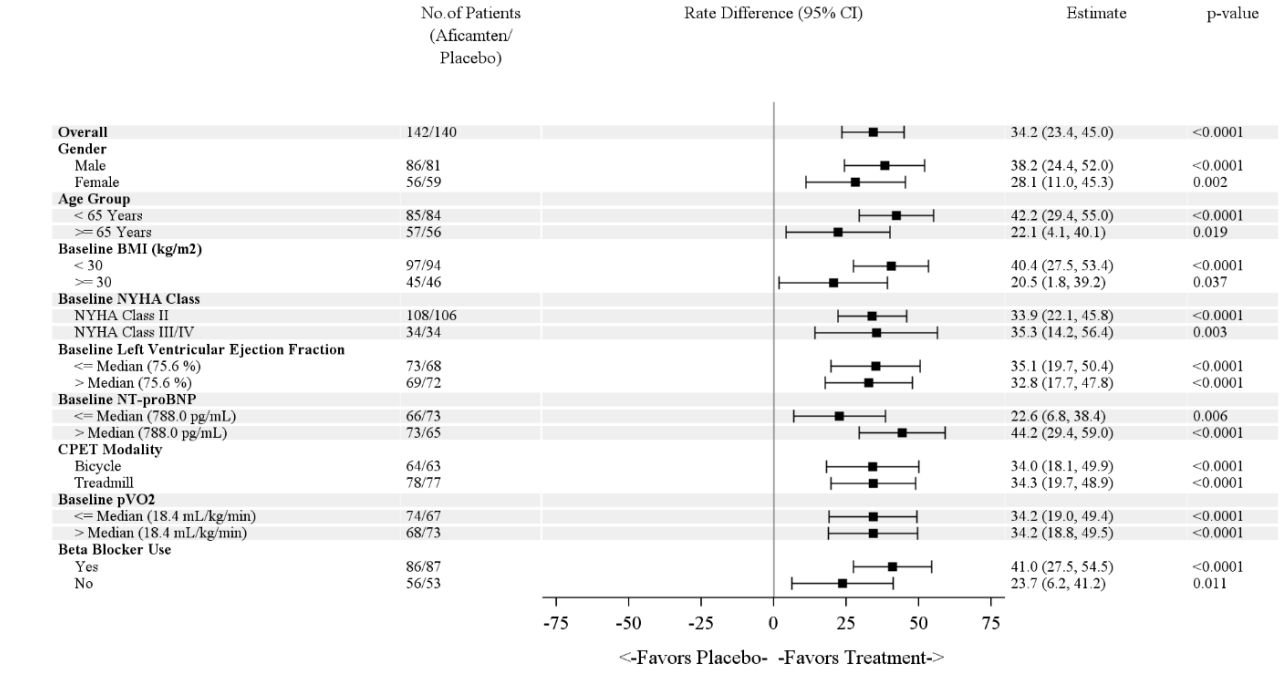


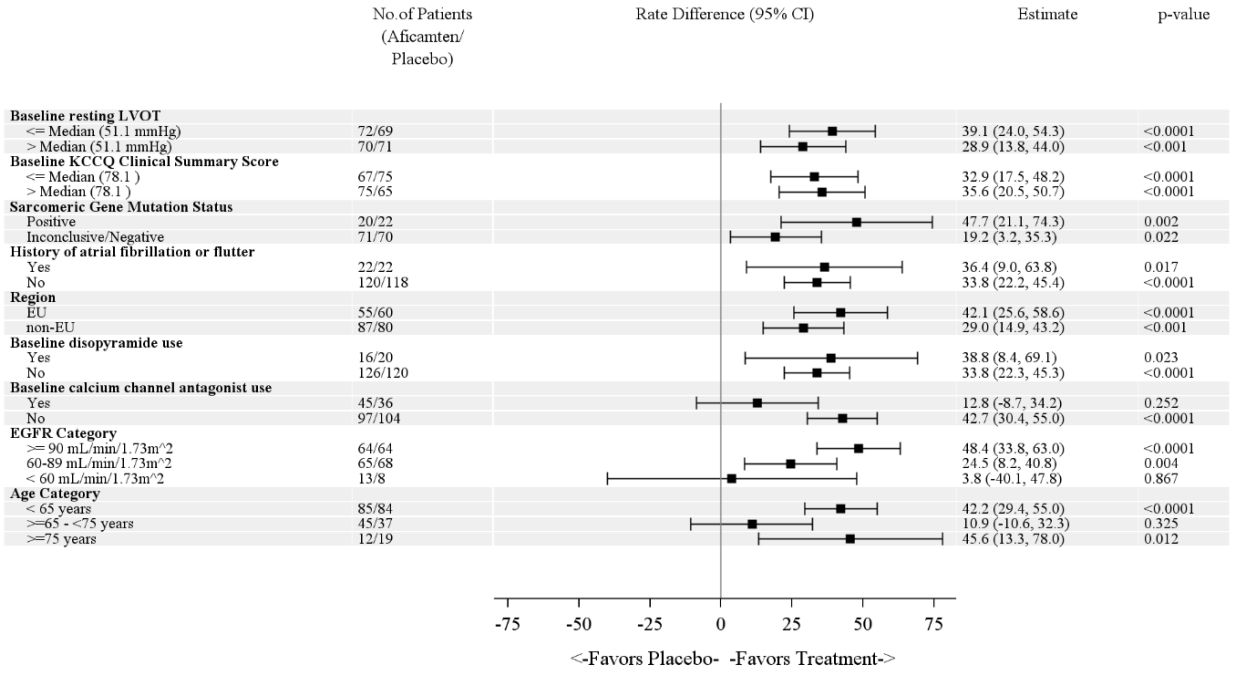
Figure 21. Forest Plot: Proportion of Participants with SRT Eligibility at Week 24 of Treatment by Subgroups



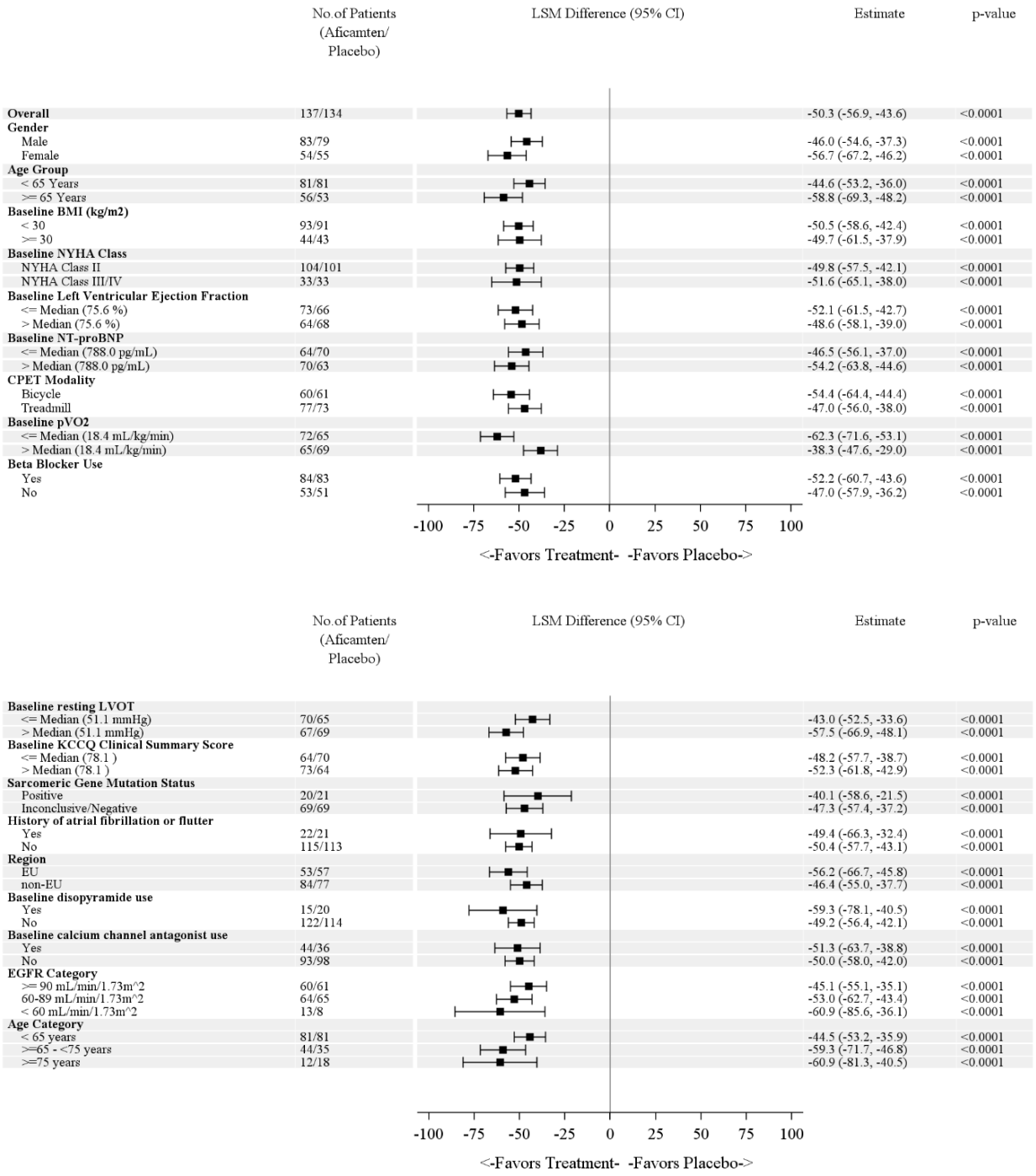


3. Figure 22. Forest Plot: Total Duration (Days) of SRT Eligibility During the 24-Week Treatment Period in Patients Who Were SRT Eligible at Baseline by Subgroups





4. Figure 23. Forest Plot: Proportion of Patients with ⩾1 Class Improvement in NYHA Class at Week 24 by Subgroups



- **Ancillary analyses**

Analyses on mortality and MACE

Although not defined as an efficacy outcome, data on mortality and MACE is shortly summarized. No patients died in either the aficamten or placebo arm during the study period. MACE occurred in 6 (4.2%) of the aficamten treated patients and in 9 (6.4%) of the placebo treated patients. The majority of MACE events in both arms was due to CV hospitalization (3 in the aficamten arm and 4 in the placebo arm). The incidence of new onset persistent AF was 1 patients in both the aficamten and placebo arm. Further details on cardiovascular outcomes is discussed in the clinical safety section.

Important protocol deviations

In response to a request of the CHMP, the Applicant performed sensitivity analyses after excluding patients with important protocol violations, as shown in Table 39. The results remained virtually unchanged.

Table 37. Sensitivity Analysis after excluding participants with Important Protocol Deviations

Visit **Statistics**	**Aficamten**	**Placebo**
pVO_2		
Baseline		
N	122	119
Mean (SD)	18.62 (4.466)	18.34 (4.363)
Change from Baseline - Week 24		
N	114	110
LS Mean (95% CI)	1.70 (1.16, 2.24)	0.08 (-0.47, 0.63)
LS Mean Diff vs. Placebo (95% CI); p-value	1.62 (0.86, 2.38); < 0.0001	
KCCQ-CSS		
Baseline		
N	122	119
Mean (SD)	76.9 (17.72)	73.3 (17.74)
Change from Baseline - Week 24		
n	120	117
LS Mean (95% CI)	11.7 (9.6, 13.9)	3.9 (1.8, 6.1)
LS Mean Diff vs. Placebo (95% CI); p-value	7.8 (4.8, 10.8); < 0.0001	
≥ 1 NYHA Class Improvement		
Week 12		
n	122	119
Yes	56 (45.9)	20 (16.8)
No	64 (52.5)	97 (81.5)
Missing	2 (1.6)	2 (1.7)
Common Rate Difference versus Placebo (95% CI); p-value	29.1 (18.2, 40.0); < 0.0001	
Week 24		
n	122	119
Yes	69 (56.6)	30 (25.2)
No	51 (41.8)	87 (73.1)
Missing	2 (1.6)	2 (1.7)
Common Rate Difference versus Placebo (95% CI); p-value	31.5 (19.7, 43.2) < 0.0001	

Visit Statistics	Aficamten	Placebo
Valsalva LVOT-G		
Baseline		
n	122	119
Mean (SD)	83.15 (31.953)	82.39 (32.097)
Change from Baseline - Week 24		
n	119	116
LS Mean (95% CI)	-49.10 (-54.24, -43.96)	1.57 (-3.64, 6.77)
LS Mean Diff vs. Placebo (95% CI); p-value	-50.67 (-57.94, 3.69); < 0.0001	
Valsalva LVOT-G < 30 mmHg		
Week 12		
n	122	119
Yes	67 (54.9)	7 (5.9)
No	53 (43.4)	110 (92.4)
Missing	2 (1.6)	2 (1.7)
Common Rate Difference versus Placebo (95% CI); p-value	49.1 (39.3, 58.9); < 0.0001	
Week 24		
n	122	119
Yes	64 (52.5)	5 (4.2)
No	56 (45.9)	112 (94.1)
Missing	2 (1.6)	2 (1.7)
Common Rate Diff vs. Placebo (95% CI); p-value	48.6 (39.0, 58.2); < 0.0001	
Total Workload During CPET		
Baseline		
n	121	118
Mean (SD)	123.2 (39.22)	123.0 (40.88)
Change from Baseline - Week 24		
n	115	109
LS Mean (95% CI)	14.1 (9.5, 18.7)	1.9 (-2.8, 6.5)
LS Mean Diff vs. Placebo (95% CI); p-value	12.2 (5.8, 18.7); < 0.001	
SRT Duration		
Week 24		
n	26	27
LS Mean (95% CI)	32.8 (15.9, 49.6)	116.9 (100.5, 133.3)
LS Mean Diff vs. Placebo (95% CI); p-value	-84.2 (-107.2, -61.2); < 0.0001	

Responder analyses based on ≥ 3 mL/kg/min Increase in pVO2 are shown in Table 40.

Table 38. Proportion of Patients with ≥ 3 mL/kg/min Increase in pVO2 from Baseline at Week 24

Visit **Statistics**	**Aficamten (N=142)**	**Placebo (N=140)**
Week 24	142	140
≥3 mL/kg/min Increase, n (%)		
Yes	37 (26.1)	13 (9.3)
No	96 (67.6)	117 (83.6)
Missing	9 (6.3)	10 (7.1)
Common Rate Difference (vs. Placebo)	16.7	
95% CI Common Rate Difference	(8.1, 25.3)	
p-value	<0.001	
Common Odds Ratio (vs. Placebo)	3.524	
Exact 95% CI of Odds Ratio	(1.717, 7.791)	
p-value	<0.001	

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Study Identifier: Pivotal Phase 3 CY 6031	
Study Design	A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety over 24 weeks of treatment with aficamten in adults with symptomatic HCM and LVOT obstruction.
Study Population	Adults with symptomatic oHCM with resting LVOT-G ≥ 30 mmHg and Valsalva LVOT-G ≥ 50 mmHg, LVEF ≥ 60%, and NYHA functional class II or III. In addition, participants had respiratory exchange ratio ≥ 1.05 and pVO_2 ≤ 90% predicted at the screening CPET.
Primary Endpoint	Change in pVO_2 by CPET from baseline to Week 24
Secondary Efficacy Endpoints	• Change in KCCQ-CSS from baseline to Week 12 and Week 24 • Proportion of participants with ≥ 1 class improvement in NYHA functional class from baseline to Week 12 and Week 24 • Change in Valsalva LVOT-G from baseline to Week 12 and Week 24 • Proportion of participants with Valsalva LVOT-G < 30 mmHg at Week 12 and Week 24 • Total duration of SRT eligibility during the 24-week treatment period in participants who were SRT eligible at baseline • Change in total workload during CPET from baseline to Week 24
Key Exploratory Efficacy Endpoints	• Proportion of participants at Week 24 achieving either change from baseline ≥ 1.5 mL/kg/min in pVO_2 and ≥ 1 class improvement in NYHA functional class OR change from baseline ≥ 3.0 mL/kg/min in pVO_2 and no worsening of NYHA functional class • Change in resting LVOT-G and LVEF from baseline to Week 24 • Change in NT-proBNP and hs-cardiac-TnI from baseline to Week 24 • Change in the EQ-5D-5L from baseline to Week 24 • Change in the SAQ-7 from baseline to Week 24 • Change in CMR measurements from baseline to Week 24
Treatment Assignments	Randomized in a 1:1 ratio to receive placebo or aficamten (5, 10, 15, or 20 mg QD), with stratification by CPET modality (treadmill or bicycle) and beta-blocker use (yes or no). The starting dose of aficamten was 5 mg QD, and the dose was individually titrated based on echocardiographic criteria (LVEF, LVOT-G).
	A total of 282 participants (142 aficamten, 140 placebo) were randomized; all 282 participants received at least 1 dose of IP. Participants treated with aficamten received treatment for a median of 169.0 days. Participants treated with placebo received treatment for a median of 170.0 days.
Efficacy Analysis Population	All 282 randomized participants were included in the efficacy analyses (full analysis set).

Key Efficacy Results

Endpoint	**Aficamten (N=142)**	**Placebo (N=140)**	**Difference (95% CI)**
Primary Endpoint			
Change in pVO_2 (mL/kg/min) at Week 24	1.76 (0.254)	0.02 (0.253)	1.74 (1.04, 2.44)

Secondary Endpoints (presented in order of hierarchal testing)			
Week 24			
Change in KCCQ-CSS	11.6 (1.01)	4.3 (1.00)	7.3 (4.6, 10.1)
Proportion of participants with ≥ 1 NYHA class improvement	83 (58.5)	34 (24.3)	OR: 4.408 (2.560, 7.598) Diff: 34.2 (23.4, 45.0)
Change in Valsalva LVOT-G (mmHg)	-48.09 (2.406)	2.16 (2.428)	-50.25 (-56.93, -43.57)
Proportion of participants with Valsalva LVOT-G < 30 mmHg	70 (49.3)	5 (3.6)	OR: 25.479 (10.107, 88.198) Diff: 45.7 (36.9, 54.5)
Duration of SRT eligibility (days)	35.3 (7.89)	113.4 (8.05)	-78.1 (-99.8, -56.3)
Week 12			
Change in KCCQ-CSS	11.1 (0.92)	4.0 (0.91)	7.0 (4.5, 9.5)
Proportion of participants with ≥ 1 NYHA class improvement	69 (48.6)	25 (17.9)	OR: 4.604 (2.559, 8.445) Diff: 30.8 (20.6, 41.0)
Change in Valsalva LVOT-G (mmHg)	-45.75 (2.416)	2.61 (2.432)	-48.36 (-55.06, -41.66)
Proportion of participants with Valsalva LVOT-G < 30 mmHg	74 (52.1)	8 (5.7)	OR: 18.041 (7.842, 44.400) Diff: 46.4 (37.3, 55.5)
Week 24			
Change in total workload during CPET (watts)	13.4 (2.12)	1.2 (2.14)	12.2 (6.4, 18.0)
Exploratory Endpoints			
Proportion of participants meeting composite endpoint of pVO_2 and NYHA functional class; Week 24	60 (42.3)	19 (13.6)	OR: 4.719 (2.552, 9.114) Diff: 28.7 (18.8, 38.6)
Proportional (geometric LS mean) change in NT-proBNP; Week 24	0.19 (0.17, 0.22)	0.97 (0.87, 1.09)	Ratio: 0.20 (0.17, 0.23)
Proportional (geometric LS mean) change in hs-cardiac-TnI; Week 24	0.57 (0.53, 0.62)	1.00 (0.92, 1.09)	Ratio: 0.57 (0.51, 0.64)
Proportion of participants who were SRT eligible at baseline, who remained SRT-eligible at Week 24, n (%)	4/32 (12.5)	14/29 (48.3)	-36.5 (-58.5, -14.5)
Proportion of participants with improvement in KCCQ-CSS (categorical analysis; Week 12)			
≥ 5 points:	90 (63.4)	70 (50.0)	13.5 (2.1, 24.8)
≥ 10 points	63 (44.4)	33 (23.6)	20.8 (10.0, 31.6)
≥ 15 points	42 (29.6)	19 (13.6)	16.1 (6.6, 25.5)
≥ 20 points	34 (23.9)	11 (7.9)	16.1 (7.9, 24.4)
Proportion of participants with improvement in KCCQ-CSS (categorical analysis; Week 24)			
≥ 5 points:	87 (61.3)	70 (50.0)	11.3 (−0.1, 22.8)
≥ 10 points	69 (48.6)	38 (27.1)	21.5 (10.6, 32.5)
≥ 15 points	42 (29.6)	19 (13.6)	16.1 (6.7, 25.4)
≥ 20 points	31 (21.8)	11 (7.9)	14.0 (6.0, 22.1)
Ad hoc Analyses			
Week 24			
Proportion of participants achieving ≥ 1 (mL/kg/min) change in pVO_2 from baseline	78 (54.9)	43 (30.7)	Common Rate Diff: 24.3 (13.1, 35.5)

Study Identifier: Pivotal Phase 3 CY 6031	
	CI = confidence interval; CPET = cardiopulmonary exercise testing; CSR = clinical study report; Diff = difference; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LS = least squares; LVOT-G = left ventricular outflow tract gradient; NYHA = New York Heart Association; OR = odds ratio; SE = standard error; SRT = septal reduction therapy. Note: LS means (SE) and LS mean difference (95% CI) presented for continuous endpoints. The number (percentage) of responders and rate difference (Diff) and common OR (exact 95% CI of the OR) are presented for binary endpoints.

2.6.5.3. Clinical studies in special populations

No studies in adolescents or children have been completed at the time of MAA. There is an ongoing study CY 6023, which is a Phase 2/3 international, multicenter, randomized, double-blind, placebo-controlled (Period 1) and open-label extension (Period 2) trial that will assess the efficacy, PK, and long-term safety and tolerability of aficamten in pediatric participants with symptomatic oHCM. The overall objective of the trial is to determine the efficacy, safety, and tolerability of administration of aficamten in both adolescents (12 to < 18 years old) and children (6 to < 12 years old) with symptomatic oHCM.

No separate studies were conducted in elderly, patients with renal impairment or patients with hepatic impairment. The number of patients studied in special populations is shown in Table 39.

A total of 21 patients (13 in aficamten and 8 in placebo) had renal impairment. No patients with hepatic impairment were studied, as hepatic impairment was among the exclusion criteria.

Regarding renal impairment, point estimates for the primary endpoint were in favour of aficamten for the primary endpoint (1.32 (-1.24, 3.89), although statistical significance was not reached. Similarly, beneficial trends were found for the secondary endpoints KCCQ change (8.1 (-2.1, 18.4)) and duration SRT eligibility (-87.1 (-153.6, -20.7)).

A total of 75 patients aged ≥ 65 - < 75 years were studied (40 aficamten, 35 placebo) and a total of 30 patients ≥ 75 years were studied (12 aficamten, 18 placebo). Patients older than 85 were excluded as the age criteria was 18-85 years.

For the primary endpoint, the point estimates were in favour for aficamten for both the patients ≥ 65 - < 75 year (1.22 (95% CI: -0.08; 2.51)) and patients ≥ 75 years (1.93 (95% CI: -0.15; 4.01)).

Furthermore, consistency of efficacy was also shown for KCCQ-CSS change from baseline in both patients ≥ 65 - < 75 year (7.1 (95% CI: 2.0; 12.2) and patients ≥ 75 years (12.2 (95% CI: 3.7; 20.7)). Similarly, consistency of efficacy was also shown for the duration SRT eligible in both patients ≥ 65 - < 75 year (-49.3 (95% CI: -82.9; -15.7) and patients ≥ 75 years (-82.6 (95% CI: -129.4; -35.7)).

Table 39. Clinical Studies in Special Populations

	Controlled Trials	Non-controlled Trials
Renal impairment* patients (Aficamten-treated number /total number)	13/21	Not applicable (CY 6031 was a controlled study)
Hepatic impairment** patients (Aficamten-treated number /total number)	0/0	Not applicable (CY 6031 was a controlled study)
Paediatric patients < 18 years (Aficamten-treated number /total number)	0/0	Not applicable (CY 6031 was a controlled study)
Age 65-74 (Aficamten-treated number /total number)	45/82	Not applicable (CY 6031 was a controlled study)
Age 75-84 (Aficamten-treated number /total number)	12/31	Not applicable (CY 6031 was a controlled study)
Age 85+ (Aficamten-treated number /total number)	0/0	Not applicable (CY 6031 was a controlled study)
Other (Aficamten-treated number /total number)	0/0	Not applicable (CY 6031 was a controlled study)

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses, nor meta-analyses were provided. The Applicant has however provided an overview comparing the results of the various studies on efficacy outcomes. These are shown in Table 39.

The descriptions of study 6021 and 6022 can be found under section 3.8 supportive studies. Study 6031 has been described in detail above.

Table 40. Cross-study Comparison of Efficacy Parameters Over Time in Aficamten-treated Participants With oHCM.

	6021 Cohort 1[a]		6021 Cohort 2[a]		6031[b]		6022[c]	
	N	Estimate	n	Estimate	n	Estimate	n	Estimate
Resting LVOT-G[d]								
Baseline, mmHg (Mean [SD])	14	53.8 (25.2)	14	58.2 (36.3)	142	54.8 (27.0)	194	48.3 (27.96)
Change from baseline (Mean [SD])								
Week 10/12[e]	14	-40.4 (26.7)	14	-43.1 (36.7)	140	-34.4 (27.4)	133	-31.5 (25.12)
Week 24	—	—	—	—	137	-34.9 (29.3)	79	-33.3 (26.72)
Week 48	—	—	—	—	—	—	45	-35.2 (29.35)
Safety follow-up[f]	14	-6.5 (24.2)	14	-13.3 (40.5)	138	-0.8 (29.7)	—	—
Valsalva LVOT-G[d]								
Baseline, mmHg (Mean [SD])	14	74.4 (25.2)	14	82.3 (36.5)	142	82.86 (31.999)	194	75.0 (28.98)
Change from baseline (Mean [SD])								
Week 10/12[e]	14	-36.4 (27.3)	14	-52.5 (44.3)	139	-44.78 (35.964)	133	-40.8 (29.05)
Week 24	—	—	—	—	137	-47.61 (37.353)	79	-43.0 (31.98)
Week 48	—	—	—	—	—	—	45	-44.2 (31.26)
Safety follow-up[f]	14	-6.4 (21.1)	14	-8.5 (26.1)	138	-4.26 (33.040)	—	—
LVEF[d]								
Baseline, % (Mean [SD])	14	73.2 (5.6)	14	75.4 (6.4)	142	74.80 (5.480)	194	72.9 (6.41)
Change from baseline (Mean [SD])								
Week 10/12[e]	13	-6.4 (7.5)	13	-11.5 (5.9)	137	-4.69 (6.958)	130	-5.3 (7.44)
Week 24	—	—	—	—	134	-6.80 (7.454)	78	-5.1 (7.37)
Week 48	—	—	—	—	—	—	44	-6.2 (7.12)
Safety follow-up[f]	14	-4.4 (7.0)	14	-2.1 (5.1)	136	-3.53 (5.783)	—	—

	6021 Cohort 1[a]		6021 Cohort 2[a]		6031[b]		6022[c]	
	N	Estimate	n	Estimate	n	Estimate	n	Estimate
Number with ≥ 1 NYHA class improvement, n (%)[d]								
Week 10/12[e]	14	6 (42.9)	14	9 (64.3)	142	69 (48.6)	131	101 (77.1)
Week 24	—	—	—	—	142	83 (58.5)	80	70 (87.5)
Week 48	—	—	—	—	—	—	45	37 (82.2)
KCCQ-CSS								
Baseline (Mean [SD])	—	—	—	—	142	75.6 (18.42)	195	70.1 (19.60)
Change from baseline (Mean [SD])	—	—	—	—				
Week 10/12[e]	—	—	—	—	140	11.1 (13.21)	125	15.9 (17.47)
Week 24	—	—	—	—	138	11.5 (13.23)	79	17.2 (17.79)
Week 48	—	—	—	—	—	—	45	13.4 (17.11)
Safety follow-up[f]	—	—	—	—	138	-3.6 (15.52)	—	—
NT-proBNP								
Baseline, pg/mL (Geo Mean [CV%])	14	344.7 (254.2)	14	695.2 (124.0)	139	734.70 (170.63)	194	789.6 (152.0)
Proportional change from baseline (Geo Mean [CV%])								
Week 10/12[e]	13	0.48 (52.76)	14	0.30 (137.75)	136	0.22 (101.38)	124	0.4 (0.36)[e]
Week 24	—	—	—	—	133	0.19 (106.10)	80	0.5 (1.06)[h]
Week 48	—	—	—	—	—	—	45	0.4 (0.39)[h]
Safety follow-up[f]	14	1.40 (77.35)	14	1.24 (118.81)	132	1.14 (60.06)	—	—

	6021 Cohort 1[a]		6021 Cohort 2[a]		6031[b]		6022[c]	
	N	Estimate	n	Estimate	n	Estimate	n	Estimate
hs-cardiac-TnI								
Baseline, pg/mL (Geo Mean [CV%])	12	28.2 (495.6)	12	9.8 (114.6)	139	17.11 (167.84)	194	14.6 (191.1)
Proportional change from baseline (Geo Mean [CV%])								
Week 10/12[e]	11	0.80 (29.44)	12	0.73 (51.88)	135	0.63 (61.99)	119	0.9 (2.10)[h]
Week 24	—	—	—	—	133	0.58 (58.25)	74	0.7 (0.36)[h]
Week 48	—	—	—	—	—	—	41	0.8 (0.48)[h]
Safety follow-up[f]	12	1.10 (42.50)	12	1.07 (45.52)	131	1.05 (72.16)	—	—

CSR = clinical study report; CV% = coefficient of variation; GeoMean = geometric mean; hs-cardiac-TnI = high sensitivity cardiac troponin I; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; NT-proBNP = -N-terminal- pro-B-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; SD = standard deviation.

[a] Data presented in CY 6021 are for the pharmacodynamic analysis set (data from Cohort 3 are not presented).

[b] Data presented in CY 6031 are for the full analysis set.

[c] Data presented in CY 6022 are for the modified efficacy analysis set.

[d] Core laboratory-reported values.

[e] Data presented are from Week 10 in CY 6021 and Week 12 in CY 6031 and CY 6022.

[f] The safety follow-up period was 2 weeks after the end of the treatment period in CY 6021 (Week 12) and 4 weeks after the end of the treatment period in CY 6031 (Week 28).

[g] Percentages were based on the number of participants in the analysis set in CY 6021 and CY 6031. Percentages were based on the number of participants at each visit in CY 6022.

[h] Mean (SD) values are presented for CY 6022.

2.6.5.6. Supportive studies

2.6.5.6.1. CY 6021

The Phase 2 Study CY 6021 provides supporting efficacy data for aficamten in participants with oHCM. Results from this study informed the dosing range and regimen to be used in the Phase 3 pivotal Study CY 6031 and the long-term extension Study CY 6022 and provided initial evidence of the efficacy of aficamten in the oHCM population.

Results for key efficacy parameters are described in the following sections for participants with oHCM in Cohorts 1 to 3 of CY 6021.

Methodology

This was a Phase 2, multi-center, randomized, placebo-controlled, double-blind, dose-finding study in participants with symptomatic HCM. The study consisted of 4 cohorts. For Cohorts 1 and 2, participants with oHCM and not receiving disopyramide were randomized 2:1 to active or placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg in Cohort 1 and 10, 20, and 30 mg in Cohort 2) or placebo based on echocardiographic guidance. Cohort 3 consisted of participants with oHCM whose background HCM therapy included disopyramide. All participants in Cohort 3 received up to 3 escalating doses of aficamten (5, 10, and 15 mg) based on echocardiographic guidance. Cohort 4 consisted of participants with non-obstructive HCM (nHCM) whose background therapy included beta-blockers and/or calcium channel blockers, either as monotherapy or combined. Participants receiving disopyramide were excluded from Cohort 4. Cohort 4 participants received up to 3 doses of aficamten (5, 10, and 15 mg), titrated based on echocardiographic guidance. In all 4 cohorts, treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Date first participant enrolled: 10 January 2020

Date last participant completed: 28 February 2023

Key efficacy results:

For participants with oHCM (Cohorts 1, 2, and 3), the following efficacy results were observed:

Participants with oHCM showed reductions in the resting LVOT-G and post-Valsalva LVOT-G from baseline at all postbaseline visits through Week 10. These values returned toward baseline within the 2-week treatment washout period. The decreases observed with aficamten were greater than those of placebo.

At Week 10, least squares (LS) mean decreases from baseline for resting LVOT-G were significantly greater with aficamten treatment in both Cohort 1 (−40.6 mmHg, p = 0.0009) and Cohort 2 (−39.9 mmHg, p = 0.001) compared with the pooled placebo group (−15.2 mmHg). – At Week 10, LS mean decreases from baseline for post-Valsalva LVOT-G were significantly greater with aficamten treatment in both Cohort 1 (−40.4 mmHg, p = 0.0005) and Cohort 2 (−50.9 mmHg, p < 0.0001) compared with the pooled placebo group (−5.1 mmHg). – At Week 10, LS mean changes in resting LVOT-G and post-Valsalva LVOT-G in Cohort 3 were −29.7 mmHg and −26.9 mmHg, respectively.

The proportion of responders, defined as both resting LVOT-G < 30 mmHg and post-Valsalva LVOT-G < 50 mmHg at Week 10, was greater among aficamten-treated participants (78.6% in Cohort 1 and 92.9% in Cohort 2) compared with placebo-treated participants (8.3%). In Cohort 3, the proportion of responders was 50.0%.

Aficamten-treated participants had modest mean reductions in LVEF from baseline through Week 10. At Week 10, LS mean decreases from baseline for LVEF were significantly greater with aficamten treatment in both Cohort 1 (−6.4%, p = 0.008) and Cohort 2 (−11.0%, p < 0.0001) compared with the LS mean change in the pooled placebo group (0.8%). An LS mean decrease from baseline was also observed in Cohort 3 at Week 10 (−5.9%). The effect of aficamten on LVEF was reversible within a 2-week washout period (ie, Week 10 to Week 12).

Improvement of at least one NYHA functional class between baseline and Week 10 was observed in 42.9% and 64.3% of participants treated with aficamten in Cohorts 1 and 2, respectively, compared with 33% of placebo-treated participants Cohorts 1 and 2. group. For Cohort 3, 83.3% of participants had improvement of at least one NYHA functional class.

At Week 10, geometric mean NT-proBNP decreased from baseline by 57% and 67% in aficamten-treated participants in Cohorts 1 and 2, respectively, compared with a 4% decrease in the pooled placebo group. In Cohort 3, geometric mean NT-proBNP decreased by 52%.

At Week 10, geometric mean high sensitivity cardiac troponin I (hs-cTnI) decreased from baseline by 19% and 28% in participants treated with aficamten in Cohorts 1 and 2, respectively, compared with 1% in the pooled placebo group. In Cohort 3, geometric mean troponin decreased by 19%.

2.6.5.6.2. CY 6022

The open-label extension Study CY 6022 provides supporting long-term efficacy data for aficamten in participants with oHCM. An objective was to assess the long-term effects of aficamten on left ventricular outflow tract gradient (LVOT-G) in participants with obstructive hypertrophic cardiomyopathy. Results for key efficacy parameters for participants with oHCM in CY 6022 at the time of the interim data cutoff (31 AUG 2024) are described in the following sections. No efficacy data from participants with nHCM were summarized in the interim analysis.

Methodology

This is an ongoing, open-label, safety and tolerability study of chronic dosing of aficamten in participants with symptomatic HCM who have participated in a previous study of aficamten, such as Phase 2 CY 6021 or Phase 3 CY 6031. Participants are administered a daily dose of aficamten. Each participant starts at the lowest dose of 5 mg and undergoes site-read echocardiography-guided dose titration to their maximum tolerated dose (not to exceed the highest prespecified dose of 20 mg). Dose adjustments may be made no more frequently than every 2 weeks. Treatment is to continue until the marketing authorization is achieved in the participant's country or the study is terminated.

Key efficacy results

A total of 213 participants with oHCM were enrolled and received treatment with aficamten. Participants with oHCM had a mean age of 60.6 years; approximately half were male (55.9%), and the majority were White (95.8%). At baseline, the mean (SD) core laboratory-reported LVEF was 72.7% (6.5), resting LVOT-G was 48.2 (28.3) mmHg, and Valsalva LVOT-G was 75.3 (29.4) mmHg. A family history of HCM was reported in 27.7% of participants, and 20.7% of participants had a known HCM-causing gene mutation.

The Applicant provided updated analyses as of 31 Aug 2024, when the total exposure to aficamten was 441.56 patient-years. This represented 178 (53.9%) participants and 46 (13.9%) participants who had at least 12 and 24 months, respectively.

Resting LVOT-G
Statistically significant reductions from baseline were observed in resting LVOT-G at Week 12 (mean change: -31.5 mmHg; $p < 0.0001$) and sustained through Week 108 (mean change: -31.3 mmHg; $p = 0.0002$). Mean resting LVOT-G decreased rapidly after initiation of aficamten treatment and persisted throughout treatment (Figure 16).

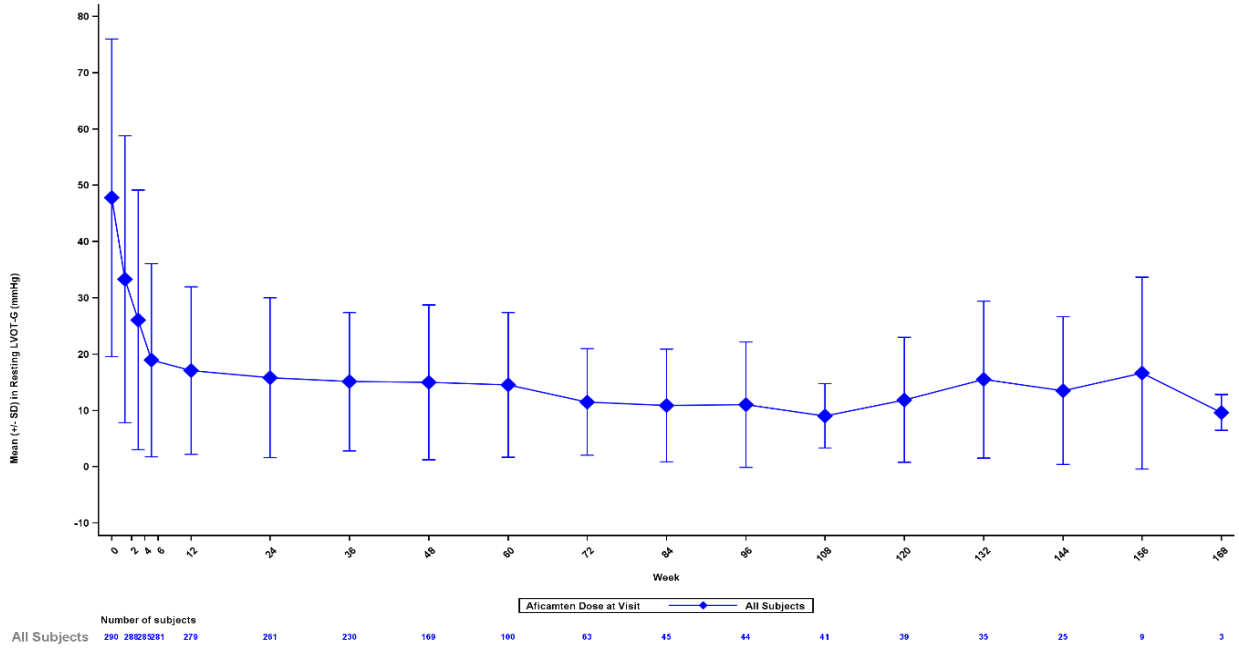


Figure 25. Mean Resting LVOT-G Over Time (CY 6022, Participants With oHCM)

Valsalva LVOT-G

Statistically significant reductions from baseline were observed in Valsalva LVOT-G at Week 12 (mean change: -40.8 mmHg; $p < 0.0001$) and sustained through Week 120 (mean change:-44.9 mmHg; $p = 0.0010$), and beyond. Similarly, mean Valsalva LVOT-G decreased rapidly after initiation of aficamten treatment and persisted throughout treatment (Figure 17).

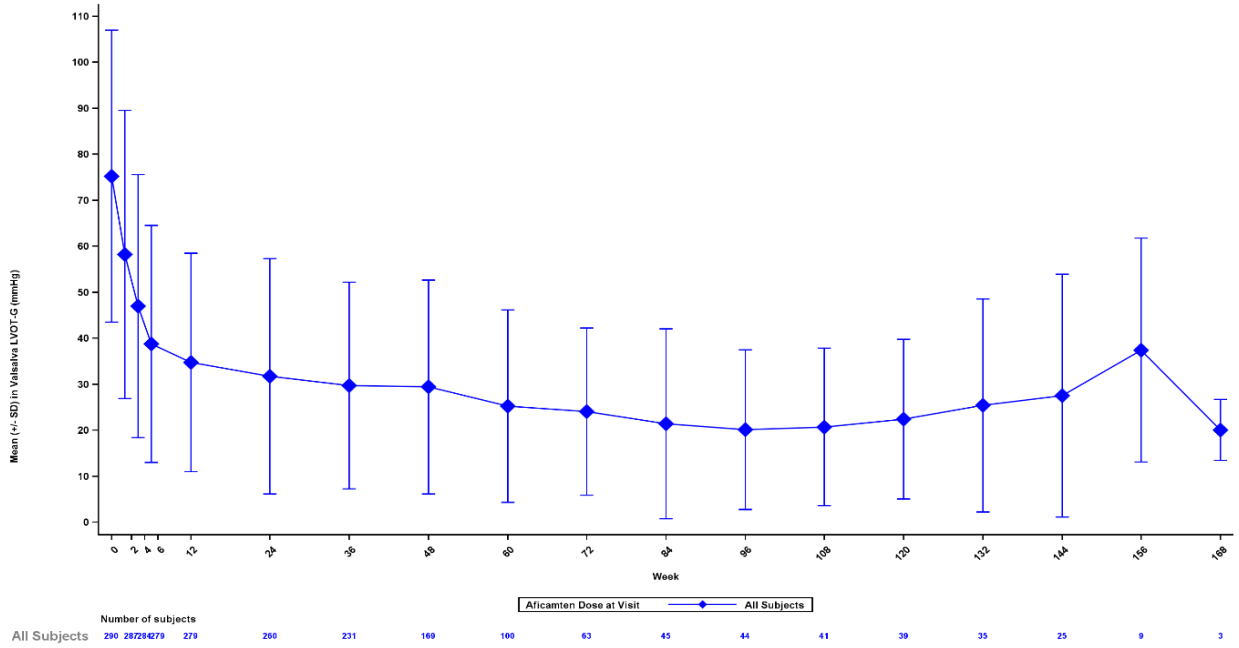


Figure 26. Mean Valsalva LVOT-G Over Time

SRT eligibility

Of the 195 participants with oHCM, 60 (30.8%) were guideline-eligible for SRT (NYHA class ≥III and resting or Valsalva LVOT-G ≥ 50 mmHg) at baseline. By Week 12, none of these participants were

eligible for SRT and at later timepoints through Week 60, only 1 or 2 participants were eligible for SRT. No participants were eligible for SRT after Week 60 through Week 120.

KCCQ

The mean KCCQ-CSS increased at Week 12 (mean change of approximately 16 points), and this improvement was maintained through week 120 and beyond, as shown in Figure 18.

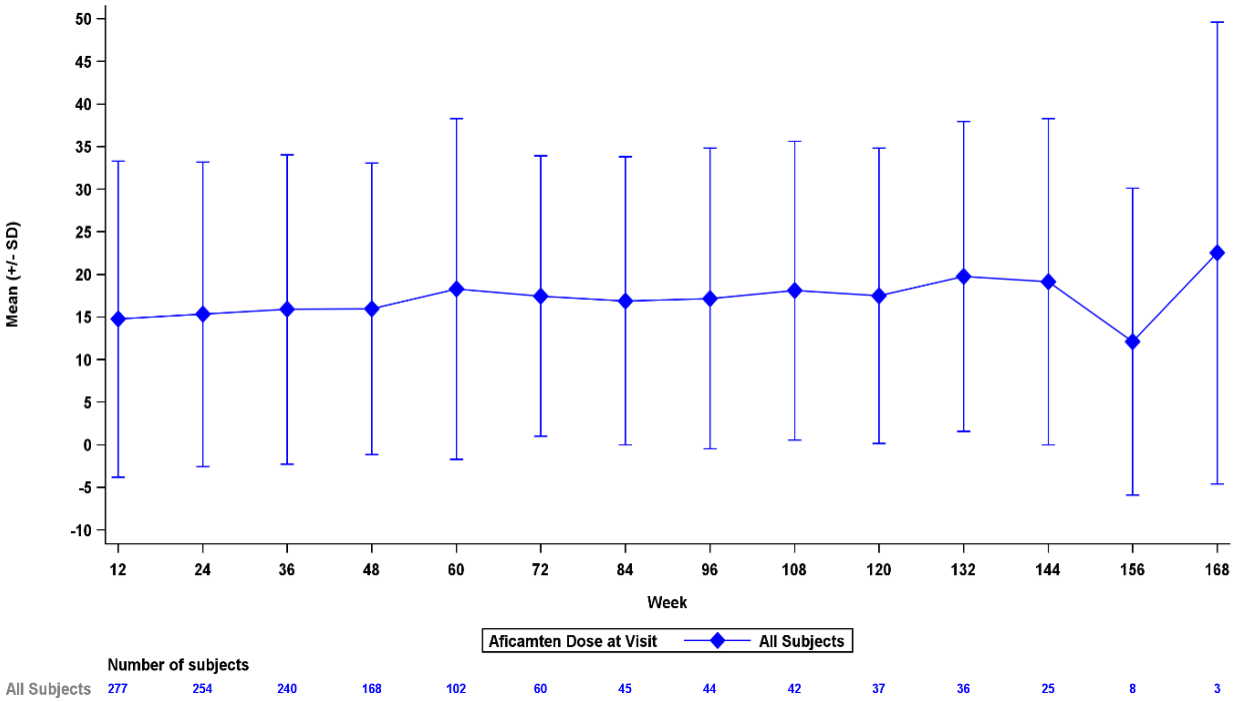


Figure 27. Mean Change in KCCQ-CSS Over Time in CY 6022 oHCM

NYHA class improvement

The proportion of participants who had at least 1 NYHA functional class improvement from baseline was 77.1% at Week 12 and 87.5% at Week 24, which was generally maintained through Week 120 (≥80.0%) and beyond, see Figure 19.

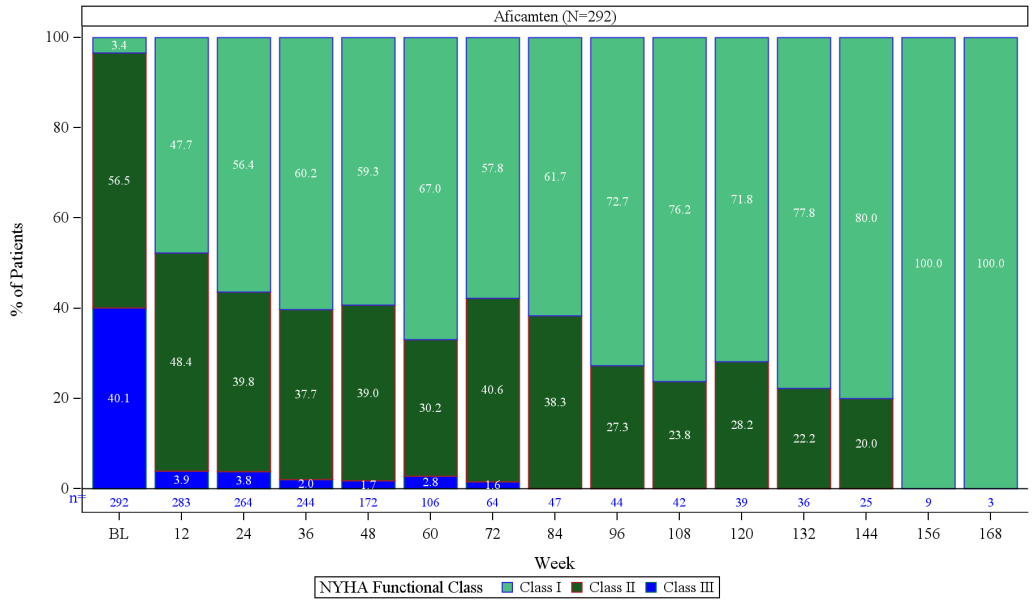


Figure 28. NYHA Functional Classification Over Time (CY 6022, Participants With oHCM)

Cardiac biomarkers

The mean proportional change from baseline in NT-proBNP was 0.4 at Week 12 and 0.5 at Week 24, with reductions ranging from 0.3 to 0.5 through Week 120. The mean proportional change from baseline in hs cardiac-TnI was 0.9 at Week 12 and 0.7 at Week 24, with reductions ranging from 0.6 to 0.9 through Week 120.

2.6.6. Discussion on clinical efficacy

Dose finding

In the first-in-human study (CY 6011), the Applicant established that single doses up to 50 mg and multiple doses up to 10 mg were both physiologically active at reducing LVEF and well-tolerated in healthy participants. Based on this, a placebo-controlled, double-blind, dose-finding phase 2 study CY 6021 was performed in patients with symptomatic HCM, where the first cohort (n=14) was started on 5 mg and escalated to 10 and 15 mg based if resting LVOT-G was ≥ 30 mmHg (or if resting LVOT-G <30mmHg: post-Valsalva LVOT-G ≥ 50 mmHg) and the biplane LVEF ≥ 50%. The 5 mg starting dose was pharmacodynamically effective and well-tolerated by all participants; however even after up titrating to 15 mg, 3 participants still had a Valsalva LVOT-G > 50 mmHg, suggesting a higher dose may have been useful in some participants. In the second cohort (n = 14 participants), higher doses of 10, 20, and 30 mg of aficamten were evaluated. The 10 and 20 mg were sufficient for the majority but two patients were up titrated to 30 mg, of which one was subsequently down-titrated and one did not meet the PD target. The Applicant suggested that the 30 mg dose is not likely to add substantial clinical benefit versus risk; therefore, 20 mg was selected as the highest dose in the Phase 3 trial. Due to the design of the dose-finding study, unfortunately no 25 mg dose was evaluated, which may potentially have been effective and tolerable.

The pivotal Phase 3 study CY 6031 followed a similar dose titration strategy as implemented in Study CY 6021; however, the LVOT-G target criteria for dose titration was simplified by focusing on the Valsalva LVOT-G only, and the target was reduced from 50 mmHg to 30 mmHg to maximize the

potential therapeutic benefit of aficamten. The stricter dose titration guidance therefore will lead to higher doses and potentially better efficacy. Importantly, in contrast to Study CY 6021, the lower limit of LVEF for dose escalation in CY 6031 was increased from 50% to 55% to provide a safety margin from the threshold of LVEF (< 50%) that triggered dose reduction in both studies. In CY 6031, participants were able to receive up to 4 increasing dose levels (5, 10, 15, and 20 mg) of aficamten over 3 dose titration opportunities, titrated at 2, 4 and 6 weeks. Dose escalation occurred only if a participant had a Valsalva LVOT-G ≥ 30 mmHg and an LVEF ≥ 55%. The dose finding strategy is considered sufficiently justified and is endorsed. Although CY 6031 is discussed in detail below, the doses reached are shortly described. Of the 142 participants treated with aficamten, the majority needed 20 mg (48.6%) or 15 mg (35.0%). These data indicate that the vast majority of patients was in need of the higher doses of 15 or 20 to achieve a sufficient pharmacodynamical response of reduction of Valsalva LVOT-G < 30mmHg. The number of participants that had to be down-titrated subsequently was very low (n=6), which is reassuring in terms of acceptability of treatment.

The goal of the proposed commercial aficamten daily dose regimen is to maintain the favourable benefit-risk profile established in the Phase 3 trial (CY 6031), while allowing for more flexible clinic visit schedules for patients with oHCM. The Applicant proposes to use the same dosing criteria for up-titrating, maintaining or reducing doses as used in CY 6031, but proposes to increase the window of echocardiography, and consequently potential dose adjustments, from 2 weeks to 2-8 weeks. To justify the larger window of echocardiography, the Applicant performed simulations which explores dose titration intervals of 2, 4, 6 or 8 weeks. Any difference in progression of LVOT-G < 30 mmHg and LVEF < 50% between the evaluated dose titration intervals appear small and limited to approximately the first 6 months of treatment, supporting the appropriateness of a 2- to 8-week window for echocardiography and potential dose adjustments in the proposed commercial dose regimen. A larger window may especially be useful for patients that are at risk of a pharmacokinetic interaction which increases half-life and thus time till steady state (reference is made to the PK section). Overall, aficamten dose titration appears to stabilize by approximately 2 years of administration with the proposed commercial dose regimen. A high probability of LVOT-G < 30 mmHg (approximately 60%) and low probability of LVEF < 50% (approximately 3%) would then be expected to persist. The Applicant proposes monitoring LVEF each 6 months (or 3 months if LVEF between 50 and 55%), which is supported by the stability of LVEF in the open label Study CY 6022, where a 3 month interval (before Amendment 6 in July 2024) and 6 month interval (after the amendment) has been used successfully (<1% had an LVEF<50% during this study).

Pivotal phase 3 trial CY 6031

Methodology

The pivotal Phase 3 study CY 6031 was a randomized, placebo-controlled, double-blind, multi-centre trial in participants with symptomatic oHCM. Key inclusion criteria were a HCM diagnosis defined by 1) LV hypertrophy with non-dilated LV chamber and 2) end-diastolic LV wall thickness ≥15 mm or ≥13 mm if gene mutation present or positive family history. Obstruction had to be present defined as a resting LVOT-G ≥30 mmHg and post-Valsalva LVOT-G ≥50 mmHg during screening. Furthermore, patients were required to have LVEF ≥ 60% and a NYHA functional class of II or III at screening. The diagnosis of oHCM is in line with the ESC guidelines. According to the ESC guideline, LVOT obstruction is defined as LVOT gradient ≥30 mmHg at rest or during physiological provocation, such as Valsalva. Additionally, a LVOT gradient of ≥50 mmHg at rest or LVOT gradient of ≥50 mmHg during Valsalva or post-exercise in symptomatic patients is usually considered to be the threshold at which LVOT obstruction becomes haemodynamically important, and treatment of LVOT obstruction is recommended. As such, the inclusion criteria identify patients with oHCM for whom (additional)

treatment is recommended according to the guideline. Since aficamten causes a reduction in LVEF, the higher criterion of LVEF>60% than the lower limit of the normal range (LVEF > 50%) was used as an inclusion criterion to ensure subject safety, which is considered appropriate. Furthermore, most oHCM patients will have a high LVEF anyway, so this likely does not have a large impact on generalizability. Patients on disopyramide were not excluded from the phase 3 trial, as data from the dose-finding Phase 2 study did not indicate an excessive effect on reducing cardiac contractility with the concomitant use of 2 negative inotropes. Key exclusion criteria were valvular heart disease, obstructive coronary artery disease, a history of LVEF < 45%, eGFR < 30 ml/min/1.73m2, hepatic impairment, prior treatment with mavacamten, and paroxysmal or permanent atrial fibrillation if rhythm restoring treatment has been required or rate control has not been achieved. Because atrial fibrillation independently modifies exercise performance and introduces variability in symptoms and biomarkers, patients with recent paroxysmal or permanent atrial fibrillation requiring rhythm-restoring treatment within six months prior to screening were excluded to minimize confounding and ensure rhythm stability throughout follow-up.

The rationale behind the exclusion of patients previously subject to SRT was to minimize potential confounding of the response to aficamten treatment due to some disease variables present in patients with inadequate response to prior SRT, such as left ventricular (LV) diastolic dysfunction, valvular abnormalities, development of coronary artery disease, medication-related symptoms, arrhythmias, persistence of pulmonary arterial hypertension, and dynamic or fixed LV obstruction. The Applicant has acknowledged, however, that in clinical practice, patients may still benefit from aficamten treatment following SRT. In fact, such patients have been included in a subsequent ongoing Phase 3 study of aficamten (CY 6032) in obstructive hypertrophic cardiomyopathy (oHCM). Nevertheless, data from this study have not yet been evaluated and therefore, evidence in this patient population remains lacking. In accordance, Section 5.1 of the Summary of Product Characteristics (SmPC) states that that no patients enrolled in the CY 6031 study had undergone prior SRT.

Eligible patients were randomized 1:1 to aficamten or placebo treatment. Randomization was stratified by use of beta-blockers (yes or no) and CPET exercise modality (treadmill or bicycle). The study was performed double blind, but because viewing echocardiogram results could have potentially compromised the blinded investigator and blinded study coordinator, only an unmasked sonographer and unmasked echocardiologist (or unmasked data entry designee) were allowed access to echocardiogram images or results for the study. There was a similar masking requirement for the NT-proBNP results. The design of CY 6031 is generally appropriate. The duration of the screening period, up to 6 weeks, is appropriate. In the randomized, double-blind treatment period of 24 weeks, participants randomized to aficamten could have received up to 4 escalating doses of investigational product over the initial 6 weeks of the trial. Participants receiving aficamten started at a dose of 5 mg once daily and could have escalated to doses of 10, 15, and 20 mg once daily if they met the escalation criteria. The dose was up-titrated to the next higher dose if on the echo Valsalva LVOT-G was ≥ 30 mmHg and the biplane LVEF ≥ 55%, otherwise, the participant remained on the same dose. Doses were reduced if LVEF < 50% and temporarily interrupted if LVEF < 40%. Patients randomized to the aficamten group were largely titrated up toward higher doses, indicating more tablets of 5 mg per day. Investigational product was packaged in blister strips that contained either 5 mg tablets of aficamten or matching placebo, which were then supplied to participants within a blister card that contained 4 blister strips. Each blister card contained a combination of active and/or placebo strips to provide the correct dose. Therefore, the blind was adequately maintained.

A CMR imaging sub-study assessed the effects of administration of aficamten dosing on cardiac morphology, function, and fibrosis in approximately 100 oHCM patients who are eligible and consent to participate. CMR was performed during screening period and at week 24.

The primary endpoint of the trial was the change in pVO2 by CPET from baseline to Week 24. Comparison was made of the aficamten group to the placebo group, with the hypothesis that there is superiority of aficamten over placebo on the primary endpoint. Although exercise testing is a clinically relevant endpoint, it is not a validated surrogate for hard endpoints such as hospitalization or mortality. However, obstructive HCM proceeds to heart failure in only 5% of the patients per year and literature data indicates a mortality of <1.0% per year. Mortality in oHCM is known to increase with symptoms, but as no NYHA IV patients are included in the study, mortality is not expected to considerably exceed the 1.0% reported for the overall oHCM population. Thus, a superiority study investigating morbidity/mortality as a primary efficacy endpoint may not be feasible within a reasonable time frame. According to the *EMA Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95, Rev.2)*, exercise capacity may be acceptable as a primary efficacy endpoint, in case the result is supported by secondary endpoints that meaningfully contribute to the understanding of the clinical relevance of the effect and the cardiovascular safety profile of the product can be adequately characterised (this part is discussed in the clinical safety section). In the primary estimand, 9 participants (6.3%) in the aficamten group and 10 participants (7.1%) in the placebo group had an intercurrent event of 'invalid test' or 'early termination not associated with an AE' and 'one early termination due to AE' in the placebo arm. The missing data due to these events was handled by a hypothetical strategy, which since they can be considered random events, is acceptable.

In terms of secondary endpoints, the Applicant investigated the change in KCCQ-CSS, improvement in NYHA classification, change in Valsalva LVOT-G, duration of eligibility for SRT and change in total workload during CPET, in hierarchical testing order. Although each of these endpoints is considered relevant for patients with oHCM, the SRT eligibility is considered especially relevant for the benefit risk, as SRT eligibility can be considered a somewhat more harder endpoint, although it is noted that it is defined by LVOT-G change and NYHA class improvement. KCCQ-CSS is also considered of importance, although the cut-off for clinical relevance is not validated in oHCM. Although the Applicant states a 5 point difference as clinically relevant, for other drugs in oHCM, the 10 point cut off has been used (e.g. mavacamten). Although defined as an exploratory endpoint by the Applicant, the number of patients still eligible for SRT at week 24, and the number of patients with an improvement in KCCQ-CSS >10 points are considered important endpoints to support the effect on exercise capacity.

Overall, the assumptions used for the sample size calculation and the planned number of patients (135 per arm) derived from these assumptions are numerically acceptable and no specific concerns are raised in this regard. However, the Applicant indicated that they had the option to monitor certain aggregated data (specifically, the pooled missing data rate and the pooled SD for the primary endpoint) in a blinded manner, with the possibility of increasing the sample size to achieve the targeted power of 90%. This was included during the conduct of the study as part of Amendment 3, which is dated on 03/01/2023 while the first patient was enrolled on 01/02/2022 and the last patient completed the study on 18/12/2023. The Applicant stated that the Amendment 3 provision was not data-driven. At the time of the inclusion of Amendment 3, 105 patients had been randomised, representing 37% of the final sample (105/282). Given that data were blinded to the Applicant and that the proportion of patients enrolled at the time of the amendment was not excessively large, this issue was not further pursued. No specific method described in either the protocol or SAP to adjust the sample size if review of blinded SD for the primary endpoint of pVO_2 exceeded the assumption of 3.5 mL/kg/min for change from baseline in pVO_2. However, the aggregate SD at all periodic assessments during the study remained below the assumption of 3.5 mL/kg/min for change from baseline in pVO_2. Thus, there was no impact to the integrity of the study.

An ANCOVA model was used to analyse the primary endpoint including the treatment group, baseline value of pVO_2, randomisation stratification factors and baseline body weight. Missing pVO2 at Week 24

regardless of type of intercurrent events was to be imputed using multiple imputation methodology under the Missing At Random (MAR) assumption for the primary analysis of the primary estimand. A sensitivity analysis was also performed using a repeated measures mixed model to pVO_2 baseline and Week 24 data. The RMMM were to include stratification factors, visit, stratification by visit, and a numeric covariate which equals 0 for both treatment groups at baseline and equals 0 for placebo at Week 24 and equals 1 for aficamten group at Week 24. Another sensitivity is also applied by using tipping point analysis by adjusting the imputed value of missing pVO2 in aficamten group by applying a range of negative shift values.

Results CY 6031

The date first participant enrolled was 01 February 2022 and the date last participant completed was 18 December 2023. A total of 543 persons were screened for the study. Of these, 261 failed screening, primarily for not satisfying the inclusion/exclusion criteria (98.9%). The entry criteria that were most frequently not met were a resting LVOT-G ≥ 30 mmHg and Valsalva LVOT-G ≥ 50 mmHg (n = 113) and an respiratory exchange ratio ≥1.05 and pVO2 ≤ 90% predicted (n = 82). The remaining screened participants (n = 282) were enrolled and randomized to treatment as follows: 142 to aficamten and 140 to placebo. All participants in both treatment groups received at least 1 dose of investigational product. Of the participants randomized to aficamten, 5 (3.5%) discontinued treatment early, 2 due to participant withdrawal, 2 due to a protocol deviation, and 1 due to an AE. Of the participants randomized to placebo, 4 (2.9%) discontinued treatment early, 2 due to an AE, 1 due to physician decision, and 1 due to COVID-19 restrictions. Overall, 137 patients in the aficamten group and 136 patients in the placebo group completed the planned dosing.

The percentage of major protocol deviations was very high, both in the aficamten (76.8%) and placebo groups (81.4%). The percentage of important protocol deviations was 16.9% for aficamten vs. 19.3% placebo. Protocol violations were generally balanced between the treatment groups. Nonetheless, a post-hoc analysis after excluding important protocol violations was provided to demonstrate that important protocol violations did not bias the outcome of the study.

Participants treated with aficamten received treatment for a median of 169.0 days. At week 8 (end of titration phase), 68 (48.6%) participants achieved an aficamten dose of 20 mg daily, 49 participants (35.0%) achieved a dose of 15 mg daily, 18 (12.9%) participants achieved a dose of 10 mg daily and 5 patients (3.6%) achieved a dose of 5 mg daily. Overall, participants had a median age of 59.5 years, with a range of 18 to 84 years. Most participants were male (59.2%), white (79.1%), and not Hispanic or Latino (91.5%). A limitation of the trial is the severe underrepresentation of Black patients (1%), with only three Black participants in the aficamten group and none in the placebo group. This mirrors the low enrolment of Black patients in the EXPLORER-HCM trial of mavacamten, whereas studies show that Black patients with HCM are diagnosed younger, have more severe symptoms, receive fewer standard treatments, and face higher mortality risks compared to White patients.

At baseline, participants had a median BMI of 28.1 kg/m^2. The majority of participants had NYHA Class II heart failure (75.9%). The mean LVEF was 74.8%, the mean resting LVOT-G was 55.1 mmHg, and the mean Valsalva LVOT-G was 83.1 mmHg. A total of 61 participants (32 aficamten, 29 placebo) were SRT eligible at baseline (defined as having NYHA Class III or IV heart failure and a resting or Valsalva LVOT-G ≥ 50 mmHg). The mean pVO2 by CPET at baseline was 18.5 mL/kg/min, with 55% of participants using treadmill as the CPET modality. Overall, 26.6% of participants had a family history of HCM, and 17.4% of participants had a known HCM-causing gene mutation (per medical history assessment) at enrolment. The median time since the initial HCM diagnosis was 4.07 years (range: 0.0–45.9 years). Beta-blockers were used by 61.3% of participants, non-dihydropyridine calcium channel blockers were used by 28.7% of participants and 12.8% of participants were taking disopyramide. The recruited participants reflect a population of symptomatic oHCM patients regarding

demographics, comorbidities and guideline-directed medical therapies for oHCM, which were well distributed across the two treatment arms, with minor exceptions regarding medication. Disopyramide use was lower in the aficamten arm (11% vs 14%), whereas use of calcium antagonists was higher (32% vs 26%). However, the Applicant provided post-hoc subgroup analyses demonstrating consistency of the treatment effect regardless of using these drugs.

With respect of the genotype, a 17.4% of the total patients had a known HCM-causing gene mutation [16.9% (n=24) in the aficamten group vs. 17.9% (n=25) in the placebo group] at enrolment, which was based on site specific history. The Applicant also did a genetic testing substudy based on DNA sample collection during the study in consenting participants (n = 184 out of 282 participants) and this reflects the results of mutation analyses conducted by a genetics core laboratory. Analyses of the primary endpoint based on mutation status in the genetic substudy indicate qualitatively similar results for the mutation positive and inconclusive/negative subgroups.

Treatment with aficamten led to a greater least squares mean change in the primary endpoint pVO2 by CPET from baseline to week 24 in the aficamten group (+1.76 mL/kg/min) than in the placebo group (+0.02 mL/kg/min), with a mean difference between treatment groups of 1.74 mL/kg/min (95% CI: 1.04, 2.44; $p < 0.0001$). This effect was consistent across all pre-specified subgroup analyses, including across the subgroup of use of a beta-blocker (yes/no), indicating efficacy even on top of already present negative inotropic medication. Similarly, in post-hoc analyses, the treatment effect was also present in patient using disopyramide, another negative inotropic medication. The Applicant also provided post-hoc requested subgroup analyses according to atrial fibrillation history, and EU vs non-EU region, which demonstrated consistency of the treatment effect across atrial fibrillation history status and region, which is reassuring. The effects of the primary endpoint were also consistent across all pre-specified sensitivity analyses, including a placebo-based imputation analysis, covid-19 impact analysis, a mixed model repeated measures analysis and a tipping point analysis demonstrating that the results remained significant through a shift to 30% of the imputed values. To demonstrate the relevance of the 1.7 ml/min increase, the Applicant provided internal and external justification. In terms of mortality and morbidity, the Applicant provided literature supporting that improvements in pVO2 has been independently shown to predict clinically relevant outcomes in oHCM, nonobstructive hypertrophic cardiomyopathy (nHCM) and systolic heart failure (Coats 2015, O'Connor 2009, Swank 2012). Although these studies have their own limitations, they do provide support for the relationship between pVO_2-increase and hard outcomes. Furthermore, the Applicant performed analyses where change in pVO2 was compared with clinically relevant anchors of NYHA Functional Class change, Patient Global Impression of Change (PGI C), and Kansas City Cardiomyopathy Questionnaire-Physical Limitation Scale (KCCQ PLS) score by the empirical cumulative distribution function (eCDF). For NYHA Functional Class, 1 and 2 class improvements were associated with median pVO2 increases of 1.1 and 1.6 mL/kg/min. For PGI-C, minimally improved and very much improved were associated with median pVO2 increases of 0.8 and 2.0 mL/kg/min. For KCCQ-PLS, a small improvement and very large improvement were associated with median pVO2 increases of 0.3 and 1.6 mL/kg/min. These results support the association between functional and symptomatic improvements in the oHCM population and support the clinical relevance of the 1.7 mL/kg/min increase of pVO2.

Regarding secondary endpoint, the Applicant performed a hierarchical testing strategy that included, in order, KCCQ-CSS, NYHA improvement, proportion Valsalva LVOT-G <30mmHg, duration of SRT eligibility and change in total workload during CPET. Each of these endpoints was met with a $P<0.0001$. Although not prespecified as secondary endpoints, during the presubmission meeting the Rapporteurs requested analyses on the number of patients still eligible for SRT at week 24 compared to baseline. From a regulatory perspective, SRT is considered a more robust ("hard") clinical endpoint, since SRT is clinically relevant to patients and clinicians as it is a highly invasive surgery associated with significant consequential risk. At baseline, 32 participants in the aficamten group and 29

participants in the placebo group were SRT eligible. Of these participants 4 (12.5%) in the aficamten group and 14 (48.3%) in the placebo group remained SRT eligible at Week 24. The common odds ratio (vs placebo) was 0.163 (95% CI: 0.031, 0.614; p = 0.005). During the 24-week treatment period, aficamten treatment resulted in a significant reduction in the time spent SRT eligible by an LS mean of −78.1 days (95% CI: −99.8, −56.3; p < 0.0001) compared with placebo.

The Applicant provided baseline characteristics of patients SRT eligible at baseline, which were generally similar by treatment group. No large differences were found that is expected to have confounded results. Upon request, the Applicant has submitted post-hoc subgroup analyses on the proportion of participants with SRT eligibility at Week 24 as well as the duration of SRT eligibility. While statistical significance was not consistently achieved across all individual subgroups, the point estimates were consistently in favour of the investigational treatment. Taken together, these results support that the observed treatment effect on reducing SRT eligibility is robust and not explained by baseline imbalances.

The Applicant has provided a listing of participants who were not SRT eligible at baseline but became SRT eligible during 24 weeks of study treatment during CY 6031. A total of 23 participants (3 aficamten; 20 placebo) became SRT eligible at any time during the study, which is reassuring and supports that aficamten is also beneficial in less compromised NYHA class II subpopulation.

The aforementioned effect on SRT eligibility was not solely driven by one of the components (LVOT-G and NYHA) as aficamten had an effect on both LVOT-G (treatment difference vs placebo was −48 mmHg (95% CI: −55, −42; p < 0.0001)) and NYHA functional class improvement (odds ratio vs placebo for ≥ 1 improvement in NYHA class was 4.41 (95% CI: 2.56, 7.60; p < 0.0001)). Another important endpoint from patients perspective is quality of life. The KCCQ clinical summary score (KCCQ-CSS) is an acceptable measure to assess quality of life of heart failure patients. A 10-point decline in KCCQ scores is considered clinically relevant and has important diagnostic significance. At week 24, 69 (48.6%) of the aficamten treated patients and 38 (27.1%) of the placebo treated patients had an improvement of ≥ 10 points in the KCCQ-CSS. The common odds ratio vs placebo for an improvement of ≥ 10 points in the KCCQ-CSS was 2.58 (1.52; 4.40); p < 0.001 in favor of aficamten. Using alternative cut-offs (5, 15, 20), comparable effects were found. The least squares mean change in KCCQ-CSS from baseline to week 24 was 11.6 points in the aficamten group and 4.3 points in the placebo group. The mean difference between treatment groups of 7.3 points was statistically significant, favoring aficamten (95% CI: 4.6, 10.1; p < 0.0001). Subgroup analyses of the secondary endpoints were provided using forest plots, demonstrating a general consistency of the treatment effects across all pre-specified subgroups. Although some subgroups did not reach statistical significance (likely due to limited sample size in certain subgroups), all point estimates were in favour of aficamten. These results further support the internal validity of the trial. Additional exploratory endpoints demonstrated that aficamten also led to significantly larger decrease in cardiac biomarkers NT-proBNP and hs-troponin I.

Finally, workload during CPET, expressed in watts, was also superior in the aficamten group compared to placebo at week 24 (LS mean difference was 12.2 watts (95% CI: 6.4, 18.0; p < 0.0001). Results from the CMR sub-study (25 patients on aficamten and 32 on placebo), demonstrated that at week 24, LV mass index, maximal LV septal wall thickness, maximal LV lateral wall thickness, and global LV max wall thickness all showed decreases from baseline in the aficamten group that were statistically significant compared to the changes observed in the placebo group.

Supportive studies

Additional support for efficacy of aficamten has been provided by results of the Phase 2 dose-finding study CY 6021. Although limited in total sample size (41 aficamten treated oHCM patients), the study demonstrated comparable beneficial effects as found in the pivotal Phase 3 study CY 6031. Aficamten treated patients demonstrated a reduction in both resting and Valsalva LVOT-G, an improvement in NYHA functional class and reductions in both NT-proBNP and cardiac troponin I. Data supporting persistence of the beneficial effects of aficamten is provided by the interim analyses of the open label extension study CY 6022. At the time of the interim data cutoff (31 October 2023), a total of 213 participants with oHCM had enrolled and had been treated by a mean of 228 days, with only 41 participants (19.2%) treated for > 60 weeks. The study demonstrated that reductions in both resting and Valsalva LVOT-G were sustained up trough week 120. Furthermore, after week 60 through week 120, none of the patients were eligible for SRT. NYHA class improvements also remained sustained up to week 120. Mean KCCQ-CSS increased from baseline and remained stable up to week 120. Lastly, reductions in both NT-proBNP and cardiac troponin I were sustained up to week 120. Unfortunately, no exercise testing was done in the open-label extension study. An updated analyses of the efficacy data from the long-term open label study was performed, indicating sustained efficacy throughout week 168.

Pooled analyses across the afore-mentioned three studies demonstrated that changes in resting and Valsalva LVOT-G, NYHA functional class improvement and cardiac biomarkers were found across each study with largely comparable estimates.

2.6.7. Conclusions on the clinical efficacy

Aficamten resulted in significant improvements in exercise capacity (pVO2max) and prevented patients from (progressing to) septal reduction therapy eligibility across the entire population of symptomatic NYHA Class II-III oHCM patients. These improvements were further supported by improvements in LVOT gradient, NYHA class, patient-reported outcomes, and cardiac biomarkers, which were maintained up to week 120, albeit with a low sample size.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Safety data collection

The key data, that establish the clinical safety profile of aficamten in participants with oHCM, comes from the pivotal phase 3 trial (CY 6031), supported by results from the Phase 2 dose-finding trial (CY 6021) and the open-label extension trial (CY 6022).

Further, an integrated analysis of safety was conducted based on data from these Phase 2 and Phase 3 studies (Integrated Summary of Safety [ISS] analysis) as described below:

- Pool 1 (placebo-controlled group) consists of participants with oHCM (ie, those treated with aficamten vs those treated with placebo) from the completed placebo-controlled trials CY 6031 and CY 6021 (2 cohorts) and provides the primary assessment for the ISS.
- Pool 2 (total oHCM exposure group) includes participants with oHCM who received aficamten in the completed trials CY 6031 and CY 6021 and/or are in the ongoing open-label extension trial, CY 6022, as of the data cutoff date of 31 Oct 2023 and provides the long-term effects of aficamten on safety parameters in patients with oHCM.

Further, pool 3 (total nHCM exposure group) includes participants with nHCM who received aficamten in the completed trial CY 6021 and/or the ongoing open label extension trial CY 6022. Analyses of Pool 3 allow comparison of the safety profile of aficamten in oHCM participants with non-oHCM participants. Also, pool 4 (phase 1 group) consists of healthy participants or participants with moderate hepatic impairment from the phase 1 studies, providing data to support the program-wide evaluation of aficamten exposure.

Participants included in the analysis

Pivotal phase 3 trial (CY 6031)

The screened participants were enrolled (n = 282) and randomized to treatment as follows: 142 to aficamten and 140 to placebo. They were all included in the safety analysis.

Integrated safety analysis – Pools 1 and 2

The integrated safety data include final data from the completed trials CY 6031 (database lock date: 21 Dec 2023) and CY 6021 (database lock date: 19 May 2023), and interim data from the ongoing trial CY 6022 (database cutoff date: 31 Aug 2024).

Of the 683 participants who received at least 1 dose of aficamten in the clinical development program, a total of 662 participants were included in an integrated safety group (Table).

Table 41: Composition of Integrated Safety Groups and Number of Participants Dosed (source: Table 4 Summary of Clinical Safety).

	Aficamten	Placebo/Other Only[a]
Pool 1 (Participants With oHCM From a Placebo-controlled Study)	170	153
CY 6031	142	140
CY 6021, Cohorts 1 and 2[b]	28	13
Pool 2 (Participants With oHCM Who Received Aficamten With or Without a Control Group)	335[c]	—
CY 6031	142	—
CY 6021, Cohorts 1, 2, and 3	41	—
CY 6032	29	—
CY 6022	296[d]	—
Pool 3 (Participants With nHCM Who Received Aficamten)	41	—
CY 6021, Cohort 4	41	—
CY 6022	34	—
Pool 4[e] (Healthy Participants and Participants With Moderate Hepatic Impairment, Phase 1 Studies)	286[e]	24[e]
Total	**662[f]**	**318[f]**

IP = investigational product; n = number of participants with an event; nHCM = nonobstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy Note: Participants could have been included in more than 1 pool. a In CY 6031 and CY 6021, participants in the control group received placebo. b In Cohort 1 of CY 6021, IP was initiated at 5 mg once daily and up-titrated in stepwise fashion to 10 then 15 mg once daily based on echocardiography-guided criteria. In Cohort 2, IP was initiated at 10 mg once daily, and up-titrated to 20 then 30 mg once daily based on echocardiography-guided criteria. c Participants were only counted once for the final count: 142 from CY 6031, 41 from CY 6021, and 100 who had been in a placebo group in either CY 6031 or CY 6021 and initiated aficamten treatment in CY 6022. d As of the data cutoff date (31 Aug 2024), CY 6022 consisted of 144 participants who had received aficamten ineither CY 6031 (n = 110) or CY 6021 (n = 34), 123 participants who had received placebo in either CY 6031(n = 112) or CY 6021 (n = 11) and initiated aficamten in CY 6022, and 29 participants from CY 6032 who had received placebo in either CY 6031 (n = 89) or CY 6021 (n = 11) and initiated aficamten in CY 6022. e Includes studies CY 6011, CY 6012, CY 6013, CY 6014, CY 6017, CY 6019, and CY 601-10. Participants exposed to both aficamten and to placebo/other are included in the aficamten column. f The pooled analyses did not include the Phase 1 study JX01001 in which 21 healthy participants received aficamten and 7 received placebo.

Extent of Exposure

Pivotal phase 3 trial (CY 6031)

Dosing information is summarized in Table . Participants treated with aficamten received treatment for a median of 169.0 days and had a median cumulative total exposure of 2384.4 mg. Participants treated with placebo received treatment for a median of 170.0 days.

Table 42: Extent of Exposure and IP Compliance (Safety Analysis Set) (Source: Table 18, CY6031 Clinical Study Report).

	Aficamten (N=142)	**Placebo (N=140)**
Total Duration of Treatment (Days)		
n	142	140
Mean (SD)	167.8 (19.94)	167.6 (22.65)
Median	169.0	170.0
Min, Max	27, 206	29, 200
Total Exposure (mg)		
n	142	140
Mean (SD)	2387.5 (655.50)	0.0 (0.00)
Median	2384.4	0.0
Min, Max	190, 3575	0, 0

Of the 142 participants treated with aficamten, 68 (48.6%) achieved an aficamten dose of 20 mg daily at Week 8. A total of 49 participants (35.0%) achieved an aficamten dose of 15 mg daily at Week 8. The Week 8 aficamten dose was 10 mg daily for 18 participants (12.9%) and 5 mg daily for 5 participants (3.6%).

Integrated safety analysis – Pools 1 and 2

In Pool 1, participants in both treatment groups received aficamten for a mean of 5.0 months (ranging from 0.9 to 6.8 months in the aficamten group and 1.0 to 6.6 months in the placebo group) (Table).

In Pool 2, the mean duration of exposure was 15.2 months (range: 0.1 to 41.5 months) (Table). The duration of exposure was > 6 months for 267 participants (79.7%), > 12 months for 198 participants (59.1%), and > 24 months for 47 participants (14.0%).

Table 43: Summary of Treatment Exposure (Pool 1 and Pool 2, Safety Analysis Set) (Source: Table 6, Summary of Clinical Safety).

	Pool 1		Pool 2
	Aficamten (N = 170)	**Placebo (N = 153)**	**Aficamten (N = 335)**
Duration of Exposure (Months)[a]			
Mean (SD)	4.99 (1.315)	5.23 (1.151)	15.24 (9.609)
Median (Min, Max)	5.55 (0.9, 6.8)	5.55 (1.0, 6.6)	13.96 (0.1, 41.5)
Q1, Q3	5.36, 5.68	5.45, 5.68	8.90, 19.06
Duration of Exposure Categories, n (%)[a]			
≤ 1 Month	1 (0.6)	1 (0.7)	8 (2.4)
>1-3 Months	30 (17.6)	15 (9.8)	18 (5.4)
>3-6 Months	133 (78.2)	130 (85.0)	42 (12.5)
>6-9 Months	6 (3.5)	7 (4.6)	17 (5.1)
>9-12 Months	0	0	52 (15.5)
>12-24 Months	0	0	151 (45.1)
>24-36 Months	0	0	29 (8.7
>36 Months	0	0	18 (5.4)
Aficamten Total Dose Administered (mg)			
Mean (SD)	2,123.9 (853.62)	—	6787.3 (4596.90)
Median (Min, Max)	2,263.1 (190, 3,575)	—	6130.0 (10, 22560)
Q1, Q3	1,547.5, 2,905.0	—	3515.0, 8980.0
Aficamten Average Daily Dose (mg/day)[b]			
Mean (SD)	13.6 (3.80)	—	14.4 (3.90)
Median (Min, Max)	13.6 (5, 23)	—	15.0 (5, 23)
Q1, Q3	10.4, 17.3	—	11.7, 17.9
Aficamten Last Daily Dose (mg), n (%)			
5	9 (5.3)	—	16 (4.8)
10	36 (21.2)	—	61 (18.2)
15	55 (32.4)	—	76 (22.7)
20	69 (40.6)	—	181 (54.0)
30	1 (0.6)	—	1 (0.3)
Dose Compliance (%)[c]			
Mean (SD)	98.9 (5.46)	99.8 (4.65)	97.6 (6.14)
Median (Min, Max)	100.0 (41, 110)	100.0 (81, 147)	99.6 (50, 110)
Q1, Q3	98.8, 100.0	99.0, 100.1	97.9, 100.0

Max = maximum; Min = minimum; N = number of participants; Q1 = first quartile; Q3 = third quartile; SD = standard deviation. a Duration of exposure is defined as time from the first dose date to the last dose date. b Aficamten average daily dose is calculated as total dose administered divided by duration of adjusted exposure (calculated as duration of exposure minus days of dose interruptions). c Aficamten dosing compliance is 100 × (number of tablets dispensed – number of tablets returned)/expected number of tablets administered

2.6.8.2. Adverse events

General information on adverse events

Pivotal phase 3 trial (CY 6031)

The participant incidence of TEAEs was balanced between treatment groups: 105 participants (73.9%) in the aficamten group compared with 99 participants (70.7%) in the placebo group (Table). Severe TEAEs were reported for 8 participants (5.6%) in the aficamten group and 10 participants (7.1%) in the placebo group. A total of 12 TESAEs were reported for 8 participants (5.6%) in the aficamten group, and 18 TESAEs were reported for 13 participants (9.3%) in the placebo group. There were no treatment-emergent deaths during the study. Few participants discontinued study treatment due to a TEAE (1 participant [0.7%] in the aficamten group and 2 participants [1.4%] in the placebo group). For most participants, TEAEs were deemed by the investigator as either mild (39.4% aficamten, 41.4% placebo) or moderate (28.9% aficamten, 22.1% placebo) in severity .

Table 44: Treatment-Emergent Adverse Events Overall Summary (Safety Analysis Set) (Source: Table 41, CY6031 Clinical Study Report).

Number (%) of Participants with the Following:	Aficamten (N=142) n (%)	Placebo (N=140) n (%)
≥ 1 TEAE	105 (73.9)	99 (70.7)
≥ 1 TESAE	8 (5.6)	13 (9.3)
≥ 1 TEAE leading to early withdrawal	1 (0.7)	2 (1.4)
≥ 1 Related TEAE	19 (13.4)	18 (12.9)
≥ 1 Moderate or severe TEAE	49 (34.5)	41 (29.3)
≥ 1 Severe TEAE	8 (5.6)	10 (7.1)
Participants who died during the study	0	0

n = number of participants with event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Integrated safety analysis – Pools 1 and 2

In Pool 1, the incidence of TEAEs was balanced between treatment groups: 74.1% of participants in the aficamten group and 71.9% of participants in the placebo group had a TEAE (Table). Severe TEAEs were reported for 4.7% of participants in the aficamten group and 7.2% of participants in the placebo group. TESAEs were reported for 5.9% of participants in the aficamten group and 9.2% of participants in the placebo group. There were no fatal TEAEs in Pool 1. Few participants discontinued IP due to a TEAE (1 participant [0.6%] in the aficamten group and 2 participants [1.3%] in the placebo group). Most TEAEs were either mild (70 participants [41.2%] aficamten, 67 participants [43.8%] placebo) or moderate (48 participants [28.2%] aficamten, 32 participants [20.9%] placebo) in severity. TEAEs were severe for 8 participants (4.7%) in the aficamten group and 11 participants (7.2%) in the placebo group. No severe TEAE was reported for >1 participant.

In Pool 2, TEAEs were reported for 80.0% of participants, most of which were mild or moderate; 35 participants (10.4%) had a severe event (Table). No participant in Pool 2 had a fatal TEAE; 24 participants (8.5%) had a TESAE; and 2 participants (0.6%) discontinued treatment due to a TEAE.

Table 45: Overall Summary of Treatment-emergent Adverse Events (Pool 1 and Pool 2; Safety Analysis Set) (Source: Table 12, Summary of Clinical Safety).

Number (%) of Participants With the Following:	Pool 1				Pool 2	
	Aficamten (N = 170) n (%)		Placebo (N = 153) n (%)		Aficamten (N = 335) n (%)	
	Incidence	EAIR[a]	Incidence	EAIR[a]	Incidence	EAIR[a]
≥ 1 TEAE	126 (74.1)	294.24	110 (71.9)	299.03	268 (80.0)	222.54
≥ 1 TESAE	10 (5.9)	12.22	14 (9.2)	18.50	45 (13.4)	11.08
≥ 1 TEAE by Maximum Severity:						
Mild	70 (41.2)	115.27	67 (43.8)	130.80	120 (35.8)	36.78
Moderate	48 (28.2)	66.01	32 (20.9)	46.57	113 (33.7)	34.70
Severe	8 (4.7)	9.76	11 (7.2)	14.29	35 (10.4)	8.66
≥ 1 TEAE Related to IP[a]	21 (12.4)	27.83	22 (14.4)	31.67	57 (17.0)	15.64
≥ 1 TESAE Related to IP[a]	0	0	0	0	1 (0.3)	0.23
≥ 1 TEAE Leading to Dose Interruption	2 (1.2)	2.42	2 (1.3)	2.59	10 (3.0)	2.31
≥ 1 TEAE Leading to Permanent Discontinuation of IP	1 (0.6)	1.20	2 (1.3)	2.56	2 (0.6)	0.45
Fatal TEAE	0	0	0	0	0	0
≥ 1 TEAE Related to COVID-19	9 (5.3)	11.24	10 (6.5)	13.19	51 (15.2)	13.02

EAIR = exposure-adjusted incidence rate; COVID-19 = coronavirus disease 2019; IP = investigational product; n = number of participants with an event; N = number of participants; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event. TEAEs are adverse events that started or worsened in the treatment-emergent period (ie, from the first dose date to the last dose date + 30 [CY 6021] or 28 [CY 6031] days). Weeks 2, 4, and 6 allowed echocardiographic-guided dose titration. Participants with multiple events in the same category were counted only once for the category. [a] Persons per 100 person-years. [b]Relationship was assessed by investigators. Treatment-related events included those with missing assessment of the causal relationship.

Common Adverse Events

Pivotal phase 3 trial (CY 6031)

The MedDRA SOCs in which TEAEs were most frequently reported were Infections and infestations (26.8% aficamten, 31.4% placebo), Nervous system disorders (20.4% aficamten, 15.0% placebo), cardiac disorders (16.9% aficamten, 15.0% placebo), and General disorders and administration site conditions (16.9% aficamten, 14.3% placebo). By MedDRA PT, the most frequently reported TEAEs were headache (7.7% aficamten, 7.1% placebo), hypertension (7.7% aficamten, 2.1% placebo), palpitations (7.0% aficamten, 2.9% placebo), and upper respiratory tract infection (6.3% aficamten, 8.6% placebo) (Table).

Table 46: Treatment-Emergent Adverse Events Reported for ≥ 5% Participants in the Aficamten or the Placebo Groups by Preferred Term (Safety Analysis Set) (Source: Table 42, CY6031 Clinical Study Report).

Preferred Term	Aficamten (N=142) n (%)	Placebo (N=140) n (%)
Number of Participants with TEAEs	105 (73.9)	99 (70.7)
Headache	11 (7.7)	10 (7.1)
Hypertension	11 (7.7)	3 (2.1)
Palpitations	10 (7.0)	4 (2.9)
Upper respiratory tract infection	9 (6.3)	12 (8.6)
COVID-19	8 (5.6)	9 (6.4)
Dyspnoea	8 (5.6)	8 (5.7)
Angina pectoris	3 (2.1)	7 (5.0)
Fatigue	3 (2.1)	7 (5.0)

COVID-19 = corona virus disease 2019; n = number of participants with event; TEAE = treatment-emergent adverse event. MedDRA version 26.0 was used for this analysis.

Integrated safety analysis – Pools 1 and 2

In Pool 1, the MedDRA system organ classes (SOCs) in which TEAEs were most frequently reported were Nervous system disorders (24.1% aficamten, 17.0% placebo), Infections and infestations (23.5% aficamten, 29.4% placebo), General disorders and administration site conditions (18.2% aficamten, 13.7% placebo), and Cardiac disorders (15.9% aficamten, 15.0% placebo). Frequently reported TEAEs in Pool 1 (i.e., those reported for ≥ 5% of participants) are summarized in Table . Those occurring more frequently in the aficamten group than the placebo group were dizziness (6.5% aficamten, 2.0% placebo), hypertension (6.5% aficamten, 2.6% placebo), dyspnoea (6.5% aficamten, 5.2% placebo), and palpitations (5.9% aficamten, 3.3% placebo).

In Pool 2, the MedDRA SOCs in which TEAEs were most frequently reported were Infections and infestations (31.8%), Nervous system disorders (23.7%), Cardiac disorders (18.7%), Gastrointestinal disorders (17.0%), and General disorders and administration site conditions (15.9%). Frequently reported TEAEs were similar to those observed in Pool 1, and included, in descending order of frequency, COVID-19 (14.3%), headache (9.9%), dyspnoea (9.0%), dizziness (8.7%), and palpitations (8.7%) (Table).

Table 47: Treatment-emergent Adverse Events Reported for ≥ 5% of Participants in Either Treatment Group by Preferred Term (Pool 1 and Pool 2, Safety Analysis Set) (Source: Table 13, Summary of Clinical Safety).

	Pool 1				Pool 2	
	Aficamten (N = 170) n (%)		Placebo (N = 153) n (%)		Aficamten (N = 335) n (%)	
Preferred Term	Incidence	EAIR[a]	Incidence	EAIR[a]	Incidence	EAIR[a]
Participants With at Least 1 TEAE	126 (74.1)	294.24	110 (71.9)	299.03	268 (80.0)	222.54
Headache	14 (8.2)	17.91	14 (9.2)	19.06	33 (9.9)	8.47
Dyspnea	11 (6.5)	13.54	8 (5.2)	10.58	30 (9.0)	7.23
Hypertension	11 (6.5)	13.78	4 (2.6)	5.19	27 (8.1)	6.54
Dizziness	11 (6.5)	13.62	3 (2.0)	3.90	29 (8.7)	7.07
Palpitations	10 (5.9)	12.48	5 (3.3)	6.51	29 (8.7)	6.91
Upper Respiratory Tract Infection	9 (5.3)	11.18	12 (7.8)	16.09	26 (7.8)	6.20
COVID-19	9 (5.3)	11.24	9 (5.9)	11.86	48 (14.3)	12.23
Nasopharyngitis	6 (3.5)	7.35	6 (3.9)	7.87	27 (8.1)	6.46
Back pain	5 (2.9)	6.09	2 (1.3)	2.58	20 (6.0)	4.63
Atrial fibrillation	4 (2.4)	4.88	5 (3.3)	6.50	20 (6.0)	4.76
Fall	1 (0.6)	1.20	3 (2.0)	3.88	17 (5.1)	4.00

COVID-19 = coronavirus disease 2019; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; N = number of participants; TEAE = treatment-emergent adverse event. TEAEs are adverse events that started or worsened in the treatment-emergent period (ie, from the first dose date to the last dose date + 30 [CY 6021] or 28 [CY 6031] days). Weeks 2, 4, and 6 allowed echocardiographic-guided dose titration. Adverse events were coded using MedDRA version 26.0 for Pool 1 and version 27.0 for Pool 2. Participants with multiple events coded to the same preferred term were counted only once for the preferred term. [a] Persons per 100 person-years.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Pivotal phase 3 trial (CY 6031)

There were no treatment-emergent fatal events reported during the study.

Integrated safety analysis – Pools 1 and 2

There were no deaths in either pool 1 or pool 2.

In Pool 3 (nHCM), 1 death (cardiac arrest) was reported. The cardiac arrest occurred during the conduct of CY 6021 in a participant with NYHA class III at baseline, a known pathogenic HCM gene mutation, and an HCM morphology of mid cavitary obstruction without apical aneurysm. The participant had a history of long QT syndrome and recurrent ventricular tachycardia/ventricular fibrillation resuscitated via discharge from an implantable cardioverter defibrillator. At the time of death, the participant was receiving aficamten at a dose of 15 mg daily. The participant had undergone

a per-protocol Week 6 evaluation 2 days prior to her death and reported overall improvements in her symptoms and functional capacity (NYHA class II); there were also improvements in both NT-proBNP (1103 to 368 pg/mL) and hs-cTnI (5.8 to < 3.5 ng/L). The Week 6 echocardiogram showed an LVEF > 70%, and the ECG showed that corrected QT interval by Fridericia's formula (QTcF) had not increased (463 msec on Day 1 and Week 6). The investigator considered that the cardiac arrest was not related to IP.

Other Serious Adverse Events

Pivotal phase 3 trial (CY 6031)

Treatment-emergent SAEs were reported for 8 participants (5.6%) in the aficamten group and 13 participants (9.3%) in the placebo group (Table); TESAEs are listed by participant. TESAEs reported for > 1 participant overall were (worsening) HCM (3 participants [2.1%] aficamten, 1 participant [0.7%] placebo) and AF (1 participant [0.7%] in each treatment group). Of note, the 3 TESAEs of (worsening) HCM in the aficamten group all occurred during the washout period.

Treatment-emergent SAEs were mild for 2 participants (both in the placebo group), moderate for 7 participants (5 aficamten, 2 placebo), and severe for 12 participants (3 aficamten, 9 placebo). No participant in the aficamten group and 2 participants in the placebo group discontinued treatment due to a TESAE.

Table 48: Treatment-Emergent Serious Adverse Events Reported for > 1 Participant Overall by System Organ Class and Preferred Term (Safety Analysis Set) (Source: Table 43, CY 6031 Clinical Study Report).

System Organ Class Preferred Teram	Aficamten (N=142) n (%)	Placebo (N=140) n (%)
Participants with TESAEs	8 (5.6)	13 (9.3)
Congenital, familial and genetic disorders	4 (2.8)	1 (0.7)
Hypertrophic cardiomyopathy	3 (2.1)	1 (0.7)
Cardiac disorders	2 (1.4)	6 (4.3)
Atrial fibrillation	1 (0.7)	1 (0.7)

n = number of participants with event; TESAE = treatment-emergent serious adverse event. MedDRA version 26.0 was used for this analysis.

Integrated safety analysis – Pools 1 and 2

In Pool 1, TESAEs were reported for 5.9% of participants in the aficamten group and 9.2% of participants in the placebo group (Table). TESAEs reported for > 1 participant were HCM (worsening symptoms) (3 participants [1.8%]) in the aficamten group and syncope (2 participants [1.3%]) in the placebo group. Notably, each of the 3 TESAEs of HCM in the aficamten group occurred during the washout period (the 28-day observation period after the last dose).

In Pool 2 13.4% of participants had a TESAE. TESAEs reported for ≥ 1% of participants were atrial fibrillation (8 participants [2.4%]) and fall (4 participants [1.2%]).

Table 49: Treatment-emergent Serious Adverse Events Reported for > 1 Participant Overall by Preferred Term (Pool 1 and Pool 2, Safety Analysis Set) (Source: Table 14, Summary of Clinical Safety).

	Pool 1				Pool 2	
	Aficamten (N = 170) n (%)		Placebo (N = 153) n (%)		Aficamten (N = 335) n (%)	
Preferred Term	Incidence	EAIR[a]	Incidence	EAIR[a]	Incidence	EAIR[a]
Participants With at Least 1 TESAE	10 (5.9)	12.22	14 (9.2)	18.50	45 (13.4)	11.08
HCM[b]	3 (1.8)	3.61	1 (0.7)	1.28	3 (0.9)	0.68
Acute Coronary Syndrome	1 (0.6)	1.20	1 (0.7)	1.28	1 (0.3)	0.23
Atrial Fibrillation	1 (0.6)	1.20	1 (0.7)	1.29	8 (2.4)	1.84
Embolic Stroke	0	0	0	0	2 (0.6)	0.46
Syncope	0	0	2 (1.3)	2.57	2 (0.6)	0.45
Fall	0	0	0	0	4 (1.2)	0.91
Acute MI	0	0	1 (0.7)	1.28	2 (0.6)	0.46
Road traffic accident	0	0	0	0	2 (0.6)	0.46

HCM = hypertrophic cardiomyopathy; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; n = number of participants with an event; N = number of participants; TESAE = treatment-emergent serious adverse event. Studies included: CY 6021 Cohorts 1 and 2 (database lock: 19 May 2023) and CY 6031 (database lock: 21 Dec 2023). TEAEs are adverse events that started or worsened in the treatment-emergent period (ie, from the first dose date to the last dose date + 30 [CY 6021] or 28 [CY 6031] days). Adverse events were coded using MedDRA version 26.0 for Pool 1 and version 27.0 for Pool 2. Participants with multiple events coded to the same preferred term were counted only once for the preferred term. [a] Persons per 100 person-years. [b] The 3 TESAEs of (worsening) HCM in the aficamten group all occurred during the washout period.

Safety Topics of Interest - Adverse events of special interest

Safety topics of interest are all discussed below:

Cardiac events - Cardiac Failure

Pivotal phase 3 trial (CY 6031)

There were no clinically significant imbalances in TEAEs of cardiac failure and other events potentially related to cardiac failure (hereafter referred to as cardiac failure TEAEs) in CY 6031 based on the broad CMQ (Table); 21 participants (14.8%) in the aficamten group and 18 participants (12.9%) in the placebo group had a cardiac failure TEAE. However, the frequency of cardiac failure TEAEs was lower in the aficamten group compared with the placebo group during the on-treatment period (8 participants [5.6%] vs 17 participants [12.1%]) and higher during the washout period (14 participants [9.9%] vs 1 participant [0.7%]), likely due to withdrawal of effective treatment with aficamten. The most frequently reported cardiac failure TEAEs overall were dyspnoea and HCM (worsening symptoms) (Table).

Integrated safety analysis – Pools 1 and 2

In Pool 1, cardiac failure TEAEs (CMQ) were more frequent in the aficamten group than in the placebo group (29 participants [17.1%] vs 19 participants [12.4%], respectively) (Table). However, because a majority of cardiac failure TEAEs in the aficamten group occurred during the washout period after

completion of treatment (Table), the on treatment incidence of these TEAEs was lower in the aficamten group than in the placebo group (13 participants [7.6%] vs 17 participants [11.1%], respectively). During the on-treatment period, frequently reported cardiac failure TEAEs were dyspnoea (5 participants [2.9%] aficamten, 7 participants [4.6%] placebo) and (worsening symptoms) HCM (0 aficamten, 4 participants [2.6%] placebo) (Table). After completion of treatment during the washout period, the overall incidence of cardiac failure TEAEs was higher in the aficamten group, with corresponding higher frequencies of dyspnoea (6 participants [3.5%] aficamten, 1 participant [0.7%] placebo) and (worsening symptoms) HCM (6 participants [3.5%] aficamten, 0 participants placebo).

The higher incidences of cardiac failure TEAEs in the aficamten group during the washout period suggest that the recurrence of symptoms related to HCM was likely due to withdrawal of effective treatment with aficamten. Exposure-adjusted incidence rates of cardiac failure TEAEs overall (i.e., during the on-treatment and washout periods) were 37.01 and 26.50 persons per 100 person-years in the aficamten and placebo groups, respectively, and exposure-adjusted incidence rates of cardiac failure TEAEs during the on treatment period were 19.23 and 27.57 persons per 100 person-years, respectively.

Most cardiac failure TEAEs were single occurrences in both treatment groups; a slightly higher proportion of participants had more than 1 occurrence of a TEAE in the placebo group, and no participant had $\geq$ 3 cardiac failure TEAEs.

In Pool 1, most cardiac failure TEAEs were mild or moderate in severity, and only a small proportion of cardiac failure TEAEs were assessed as related to IP, with slightly more treatment-related TEAEs in the aficamten group than in the placebo group (Table).

While most cardiac failure TEAEs in Pool 1 were nonserious, serious events were reported in 3 participants in each treatment group with similar incidence (1.8% and 2.0% in the aficamten and placebo groups, respectively) (Table). All serious events in the aficamten group occurred during the washout period, and all serious events in the placebo group occurred during the on treatment period. As such, the exposure-adjusted incidence rates during the on-treatment period was 0 for the aficamten group and 3.87 persons per 100 person-years for the placebo group.

The participant incidence of cardiac failure TEAEs remained constant over time (Pool 2) and appeared similar in participants with nHCM (Pool 3). In Pool 2 and Pool 3, most cardiac failure TEAEs occurred only once, with few instances of recurrence. The exposure-adjusted incidence rate of cardiac failure TEAEs for aficamten in Pool 2 (14.89 persons per 100 person-years) was lower than that of the aficamten group in Pool 1 (37.01 persons per 100 person-years), suggesting that there is not a cumulative risk of cardiac failure with increasing duration of exposure.

Across all pools, there were no deaths due to cardiac failure TEAEs, and no participant discontinued aficamten due to cardiac failure TEAEs.

A focused assessment of cardiac failure TEAEs based on a narrow Cardiac failure SMQ shows a similar profile as the broad CMQ with higher frequencies reported during the washout period than the on treatment period for aficamten-treated participants in CY 6031 and Pool 1 (Table).

Table 50: Treatment-emergent Cardiac Failure Events, CMQ (Safety Analysis Set) (Source: Table 18, Summary of Clinical Safety).

Cardiac Failure CMQ Preferred Term	CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N = 142)	Placebo (N = 140)	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 335)	Aficamten (N = 41)
Participants With Any TEAE at Any Time During the Study	21 (14.8)	18 (12.9)	29 (17.1)	19 (12.4)	57 (17.0)	8 (19.5)
EAIR (persons per 100 person-years)	29.19	26.38	37.01	26.50	14.89	13.86
Participants With Any TEAE On-treatment	8 (5.6)	17 (12.1)	13 (7.6)	17 (11.1)	41 (12.2)	8 (19.5)
Participants With Any TEAE During Washout	14 (9.9)	1 (0.7)	17 (10.0)	2 (1.3)	19 (5.7)	0
Acute LV Failure	0	0	0	0	0	1 (2.4)
Cardiac Failure	3 (2.1)	0	3 (1.8)	0	3 (0.9)	0
Cardiac Failure Chronic	0	0	0	0	1 (0.3)	0
Cardiac Failure Congestive	0	1 (0.7)	0	1 (0.7)	0	1 (2.4)
Dyspnoea	8 (5.6)	8 (5.7)	11 (6.5)	8 (5.2)	30 (9.0)	5 (12.2)
Dyspnoea Exertional	1 (0.7)	1 (0.7)	2 (1.2)	1 (0.7)	3 (0.9)	0
Ejection Fraction Decreased	0	0	0	0	1 (0.3)	1 (2.4)
Gravitational Oedema	1 (0.7)	0	1 (0.6)	0	1 (0.3)	0
HCM	6 (4.2)	4 (2.9)	6 (3.5)	4 (2.6)	6 (1.8)	0
HF with preserved EF	1 (0.7)	0	1 (0.6)	0	2 (0.6)	0
HF with reduced EF	0	0	0	0	1 (0.3)	1 (2.4)
LV failure	0	0	0	0	2 (0.6)	0
NT-proBNP Increased	0	0	1 (0.6)	0	3 (0.9)	0
Oedema	1 (0.7)	2 (1.4)	1 (0.6)	2 (1.3)	1 (0.3)	0
Oedema Peripheral	1 (0.7)	2 (1.4)	2 (1.2)	2 (1.3)	6 (1.8)	0
Orthopnoea	0	0	0	0	1 (0.3)	0
Peripheral Swelling	0	2 (1.4)	2 (1.2)	2 (1.3)	3 (0.9)	0
Pulmonary congestion	0	0	0	0	1 (0.3)	0
Pulmonary Oedema	1 (0.7)	0	1 (0.6)	1 (0.7)	1 (0.3)	0
Stress Cardiomyopathy	0	0	0	1 (0.7)	0	0
Ventricular Dysfunction	0	0	0	0	0	1 (2.4)
Nonserious TEAE	18 (12.7)	17 (12.1)	26 (15.3)	17 (11.1)	53 (15.8)	7 (17.1)
Mild/Moderate TEAEs	20 (14.1)	18 (12.9)	28 (16.5)	19 (12.4)	55 (16.4)	7 (17.1)
Severe TEAEs	1 (0.7)	0	1 (0.6)	1 (0.7)	4 (1.2)	3 (7.3)
Serious TEAEs	3 (2.1)	2 (1.4)	3 (1.8)	3 (2.0)	4 (1.2)	3 (7.3)
Fatal TEAEs	0	0	0	0	0	0
TEAEs Leading to Discontinuation of IP	0	0	0	0	0	0
TEAEs Related to IP	5 (3.5)	2 (1.4)	5 (2.9)	2 (1.3)	8 (2.4)	5 (12.2)
Onset Latency (Days)	8-211	10-180	5-211	10-180	5-1014	10-530

CMQ = customized MedDRA query (consisting of Cardiac failure SMQ broad + other preferred terms); EAIR = exposure-adjusted incidence rate; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; HF = heart failure; I IP = investigational product; LV = left ventricular; MedDRA = Medical Dictionary for Regulatory Activities; N =

number of participants; NT proBNP = N-terminal pro-B-type natriuretic peptide; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

Table 51: Treatment-emergent Cardiac Failure CMQ by Treatment Status (Pool 1, Safety Analysis Set) (Source: Table 19, Summary of Clinical Safety).

Cardiac Failure CMQ Preferred Term	TEAE: On-Treatment		TEAE: Washout Period	
	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 170)	Placebo (N = 153)
Participants With Any TEAE	13 (7.6)	17 (11.1)	17 (10.0)	2 (1.3)
Cardiac Failure	1 (0.6)	0	2 (1.2)	0
Cardiac Failure Congestive	0	1 (0.7)	0	0
Dyspnea	5 (2.9)	7 (4.6)	6 (3.5)	1 (0.7)
Dyspnea Exertional	1 (0.6)	1 (0.7)	1 (0.6)	0
Gravitational Oedema	1 (0.6)	0	0	0
HCM	0	4 (2.6)	6 (3.5)	0
NT-proBNP Increased	0	0	1 (0.6)	0
Oedema	1 (0.6)	2 (1.3)	0	0
Oedema Peripheral	2 (1.2)	2 (1.3)	0	0
Peripheral Swelling	2 (1.2)	2 (1.3)	0	0
Pulmonary Oedema	0	0	1 (0.6)	1 (0.7)
Stress Cardiomyopathy	0	0	0	1 (0.7)

CMQ = customized MedDRA query (consisting of Cardiac failure SMQ broad + other preferred terms); HCM = hypertrophic cardiomyopathy; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; NT proBNP = N-terminal pro-B-type natriuretic peptide; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

Table 52: Treatment-emergent Cardiac Failure Events, Narrow SMQ (Safety Analysis Set) (Source: Table 20, Summary of Clinical Safety).

Cardiac Failure SMQ (Narrow) Preferred Term	CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N = 142)	Placebo (N = 140)	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 335)	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)	11 (3.3)	3 (7.3)
EAIR (persons per 100 person-years)	5.33	1.35	4.84	2.58	2.55	4.81
Participants With Any TEAE On-treatment	1 (0.7)	1 (0.7)	1 (0.6)	1 (0.7)	7 (2.1)	3 (7.3)
Participants With Any TEAE During Washout	3 (2.1)	0	3 (1.8)	1 (0.7)	4 (1.2)	0
Acute LV Failure	0	0	0	0	0	1 (2.4)
Cardiac Failure	3 (2.1)	0	3 (1.8)	0	3 (0.9)	0
Cardiac Failure Chronic	0	0	0	0	1 (0.3)	0
Cardiac Failure Congestive	0	1 (0.7)	0	1 (0.7)	0	1 (2.4)
Ejection Fraction Decreased	0	0	0	0	1 (0.3)	1 (2.4)
Heart failure with preserved ejection fraction	0	0	0	0	2 (0.6)	0
Heart failure with reduced ejection fraction	0	0	0	0	1 (0.3)	1 (2.4)
LV failure	0	0	0	0	2 (0.6)	0
Pulmonary Oedema	1 (0.7)	0	1 (0.6)	1 (0.7)	1 (0.3)	0
Nonserious TEAE	4 (2.8)	1 (0.7)	4 (2.4)	1 (0.7)	11 (3.3)	2 (2.9)
Mild/Moderate TEAEs	4 (2.8)	1 (0.7)	4 (2.4)	2 (1.3)	11 (3.3)	2 (4.9)
Severe TEAEs	0	0	0	0	0	3 (7.3)
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 Discontinuation of IP	0	0	0	0	0	0
TEAEs Related to IP	3 (2.1)	0	3 (1.8)	0	5 (1.5)	2 (4.9)
Onset Latency (Days)	86-192	26-136	86-192	26-136	86-608	116-522

EAIR = exposure-adjusted incidence rate; IP = investigational product; LV = left ventricular; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

Cardiac events - Major Adverse Cardiac Events (MACE)

Pivotal phase 3 trial (CY 6031)

For this analysis, MACE included AEs related to cardiovascular (CV) hospitalization, non-fatal myocardial infarction, non-fatal stroke, CV death, and cardiac arrest. A small number of participants experienced MACE in CY 6031. A higher proportion of participants in the placebo group had at least one MACE compared to the aficamten group. MACE primarily consisted of CV hospitalization and non-

fatal myocardial infarction. One participant in each treatment group had a non-fatal stroke. No participant had either CV death or cardiac arrest.

Integrated safety analysis – Pools 1 and 2

There was no clinically meaningful difference between the treatment groups for Pool 1 on the incidence of MACE, consistent with the results reported in CY 6031. CV hospitalization and non-fatal myocardial infarction accounting for the majority of the events. The incidence of MACE in aficamten-treated participants in Pool 2 was consistent with those reported for placebo-treated participants in both CY 6031 and Pool 1. These results indicate that there is no detrimental effect on MACE from aficamten treatment.

Table 53: Summary of Treatment-Emergent MACEs in CY 6031 and by Pools (Source: Table 21, Clinical Summary of Safety).

	CY 6031		Pool 1		Pool 2
	Aficamten (N=142) n (%)	Placebo (N=140) n (%)	Aficamten (N=170) n (%)	Placebo (N=153) n (%)	Aficamten (N=335) n (%)
Incidence of MACE	6 (4.2)	8 (5.7)	8 (4.7)	9 (5.9)	28 (8.4)
EAIR for any MACE (persons per 100 person-years)	8.09	10.96	9.81	11.77	6.72
CV hospitalization [a]	3 (2.1)	4 (2.9)	3 (1.8)	5 (3.3)	18 (5.4)
EAIR for CV hospitalization (persons per 100 person-years)	4.01	5.41	3.64	6.46	4.23
Acute coronary syndrome	0	1 (0.7)	0	1 (0.7)	0
Acute myocardial infarction	0	1 (0.7)	0	1 (0.7)	2 (0.6)
Arrhythmia supraventricular	1 (0.7)	0	1 (0.6)	0	1 (0.3)
Atrial fibrillation	1 (0.7)	0	1 (0.6)	0	6 (1.8)
Cardiac failure congestive	0	1 (0.7)	0	1 (0.7)	0
Carotid artery stenosis	1 (0.7)	0	1 (0.6)	0	1 (0.3)
Embolic Stroke	0	0	0	0	2 (0.6)
Gastrointestinal vascular malformation haemorrhagic	0	0	0	0	1 (0.3)
Hypertensive urgency	0	0	0	0	1 (0.3)
Hypotension	0	0	0	1 (0.7)	0
Ischaemic stroke	1 (0.7)	0	1 (0.6)	0	1 (0.3)
Middle cerebral artery stroke	0	0	0	0	1 (0.3)
Pulmonary oedema	0	0	0	1 (0.7)	0
Sinoatrial block	0	1 (0.7)	0	1 (0.7)	0
Stress cardiomyopathy	0	0	0	1 (0.7)	0
Subdural haematoma	0	0	0	0	1 (0.3)
Subdural haemorrhage	0	0	0	0	1 (0.3)
Syncope	0	1 (0.7)	0	2 (1.3)	2 (0.6)
Nonfatal MI [b]	3 (2.1)	5 (3.6)	5 (2.9)	5 (3.3)	13 (3.9)
EAIR for nonfatal MI (persons per 100 person-years)	4.00	6.81	6.07	6.50	3.02
Acute coronary syndrome	0	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.3)
Acute myocardial infarction	0	1 (0.7)	0	1 (0.7)	3 (0.9)
Blood creatine phosphokinase increased	0	1 (0.7)	1 (0.6)	1 (0.7)	3 (0.9)

ECG ST segment abnormal	1 (0.7)	0	1 (0.6)	0	1 (0.3)
ECG ST segment elevation	0	0	0	0	1 (0.3)
Troponin I increased	1 (0.7)	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.3)
Troponin T increased	0	1 (0.7)	0	1 (0.7)	0
Troponin increased	1 (0.7)	0	1 (0.6)	0	4 (1.2)
Nonfatal stroke [c]	1 (0.7)	1 (0.7)	1 (0.6)	1 (0.7)	6 (1.8)
EAIR for nonfatal stroke (persons per 100 person-years)	1.32	1.34	1.20	1.28	1.38
Carotid artery stenosis	1 (0.7)	0	1 (0.6)	0	2 (0.6)
Cerebral ischemia	0	1 (0.7)	0	1 (0.7)	0
Embolic stroke	0	0	0	0	2 (0.6)
Ischaemic stroke	1 (0.7)	0	1 (0.6)	0	1 (0.3)
Middle cerebral artery stroke	0	0	0	0	1 (0.3)
Subdural haematoma	0	0	0	0	1 (0.3)
CV death [a]	0	0	0	0	0
Cardiac arrest [a]	0	0	0	0	0

CV = cardiovascular; ECG = electrocardiogram; MACE = major adverse cardiac events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; PT = preferred term; SMQB = standardized MedDRA query broad; SMQN = standardized MedDRA query narrow. Notes: 1. Studies included in Pool 1 are CY 6021 cohorts 1, 2 (database lock date 19MAY2023) and CY 6031 (database lock date 21DEC2023). Studies included in Pool 2 are CY 6021 cohorts 1, 2, 3, CY 6031, and CY 6022 (data cutoff date 31AUG2024). Studies included in Pool 3 are CY 6021 cohort 4 and CY 6022. 2. N = number of subjects received at least one dose of CK-274 or all Placebo for CY 6031 and Pool 1. N = number of subjects received at least one dose of CK-274 in any of the studies for Pools 2 and 3. Percentages are based on N, unless otherwise specified. 3. TEAEs are adverse events that started or worsened in the TE period. TE period is from the first dose date to the last dose date + 30 (CY 6021) or 28 (CY 6031, CY 6022) days. Last dose date is as reported for patients who completed or discontinued the study, or the Data Cutoff date for ongoing patients. Weeks 2, 4, 6 in all studies and week 12/every 12 weeks afterwards in CY 6022 allow echocardiographic-guided dose titration. 4. Adverse events were coded per Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 26.0 for CY 6031 and Pool 1 and version 27.0 for Pool 2. 5. Patients with multiple events coded to the same PT were counted only once for the PT. 6. Concurrent event is defined as core lab or local LVEFs that measured prior to the MACE or during the event. Onset latency presents the range of AE onset relative to the first dose date in the study/pool. a customized PT search. b Myocardial infarction SMQB. c Ischemic central nervous system vascular conditions SMQN and hemorrhagic central nervous system vascular conditions SMQN.

Cardiac events - Ventricular Tachyarrhythmia

Pivotal phase 3 trial (CY 6031)

The incidence of ventricular tachyarrhythmia TEAE was 1.4% in the aficamten group and 3.6% in the placebo group.

Integrated safety analysis – Pools 1 and 2

In Pool 1, the participant incidence of ventricular tachyarrhythmia TEAE was 1.8% in the aficamten group and 3.9% in the placebo group (Table). Severe and serious TEAEs of ventricular tachyarrhythmia were reported at a higher frequency in the placebo group (4 participants [2.6%]) than the aficamten group (0 participants). One participant in the placebo group discontinued treatment due to a ventricular tachyarrhythmia TEAE.

In Pool 1 and Pool 2, there were no deaths due to ventricular tachyarrhythmias.

Table 54: Treatment-emergent Ventricular Tachyarrhythmia Events (Safety Analysis Set) (Source: Table 22, Summary of Clinical Safety).

Ventricular Tachyarrhythmia CMQ Preferred Term	CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N = 142)	Placebo (N = 140)	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 335)	Aficamten (N = 41)
Participants With Any TEAE	2 (1.4)	5 (3.6)	3 (1.8)	6 (3.9)	11 (3.3)	3 (7.3)
EAIR (persons per 100 person-years)	4.01	6.78	4.87	7.78	2.54	4.71
Cardiac Arrest	0	0	0	0	0	1 (2.4)
Loss of Consciousness	0	1 (0.7)	0	1 (0.7)	0	1 (2.4)
Syncope	2 (1.4)	3 (2.1)	3 (1.8)	4 (2.6)	7 (2.1)	1 (2.4)
Ventricular extrasystoles	1 (0.7)	2 (1.4)	1 (0.6)	2 (1.3	1 (0.3)	0
Ventricular Fibrillation	0	1 (0.7)	0	1 (0.7)	0	0
Ventricular Tachycardia	0	0	0	0	3 (0.9)	1 (2.4)
Nonserious TEAE	2 (1.4)	2 (1.4)	3 (1.8)	3 (2.0)	9 (2.7)	2 (4.9)
Mild TEAEs	2 (1.4)	1 (0.7)	3 (1.8)	1 (0.7)	6 (1.8)	0
Moderate TEAEs	0	1 (0.7)	0	2 (1.3)	4 (1.2)	2 (4.9)
Severe TEAEs	0	3 (2.1)	0	4 (2.6)	1 (0.3)	1 (2.4)
Serious TEAEs	0	3 (2.1)	0	4 (2.6)	2 (0.6)	1 (2.4)
Fatal TEAEs	0	0	0	0	0	1 (2.4)
TEAEs Leading to Discontinuation of IP	0	1 (0.7)	0	1 (0.7)	0	0
TEAEs Related to IP	0	0	0	0	0	1 (2.4)
History of Ventricular Tachyarrhythmia	0	3 (2.1)	0	3 (2.0)	1 (0.3)	2 (4.9)
Concurrent Decreased LVEF < 50%	0	0	0	0	0	0
Event Started After EOT	0	0	0	1 (0.7)	0	0
Onset Latency (Days)	59-162	29-172	10-162	29-172	10-907	45-363

CMQ = customized MedDRA query; EAIR = exposure-adjusted incidence rate; EOT = end of treatment; IP = investigational product; L; LVEF = left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; TEAE = treatment-emergent adverse event

Cardiac events - Supraventricular Tachyarrhythmia

Pivotal phase 3 study (CY 6031)

New onset persistent AF was reported for 1 participant (0.7%) in each treatment group.

Integrated safety analysis – Pools 1 and 2

Events of supraventricular tachyarrhythmias with focus on atrial fibrillation were summarized using a CMQ generated by including additional PTs to the SMQ of Supraventricular tachyarrhythmias (Table).

In Pool 1, the participant incidence of supraventricular tachyarrhythmia events was similar between treatment groups (7 participants [4.1%] aficamten, 6 participants [3.9%] placebo). Atrial fibrillation (4 participants [2.4%] aficamten, 5 participants [3.3%] placebo) was the most frequently reported supraventricular tachyarrhythmia TEAE; most atrial fibrillation events occurred while participants were on treatment (4 participants [2.4%] aficamten, 4 participants [2.6%] placebo). All TEAEs of

supraventricular tachyarrhythmias were mild or moderate in severity. Two participants in the aficamten group had a serious event: 1 atrial fibrillation and 1 supraventricular tachyarrhythmia; 1 participant in the placebo group had a serious event of atrial fibrillation. One nonserious, mild event of atrial fibrillation was the only supraventricular tachyarrhythmia considered by the investigator as related to aficamten. No event of supraventricular tachyarrhythmia had a fatal outcome or led to discontinuation of IP. The onset of supraventricular tachyarrhythmia events occurred from 9 to 168 days after initiation of aficamten and was similar to that observed in the placebo group.

In Pool 2, 26 participants (7.8%) had a supraventricular tachyarrhythmia event, the most common of which was atrial fibrillation (20 participants [6.0%]). Most events of supraventricular tachyarrhythmia (including atrial fibrillation) were mild or moderate in severity, nonserious, and considered by the investigator as not related to aficamten (Table). No event of supraventricular tachyarrhythmia had a fatal outcome or led to discontinuation of IP. The onset of supraventricular tachyarrhythmia events occurred from 1 to 672 days after initiation of aficamten.

Table 55:Treatment-emergent Supraventricular Tachyarrhythmia Events (Safety Analysis Set) (Source: Table 23, Summary of Clinical Safety).

Supraventricular Tachyarrhythmia CMQ Preferred Term	CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N = 142)	Placebo (N = 140)	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 335)	Aficamten (N = 41)
Participants With Any TEAE	7 (4.9)	5 (3.6)	7 (4.1)	6 (3.9)	26 (7.8)	6 (14.6)
EAIR (persons per 100 person-years)	9.52	6.85	8.63	7.84	6.29	10.09
Arrhythmia Supraventricular	2 (1.4)	0	2 (1.2)	0	2 (0.6)	0
Atrial Fibrillation	4 (2.8)	4 (2.9)	4 (2.4)	5 (3.3)	20 (6.0)	4 (9.8)
Atrial Flutter	0	0	0	0	2 (0.6)	1 (2.4)
Sinus tachycardia	0	0	0	0	1 (0.3)	0
Supraventricular Extrasystoles	2 (1.4)	1 (0.7)	2 (1.2)	1 (0.7)	2 (0.6)	0
Supraventricular Tachycardia	0	0	0	0	2 (0.6)	1 (2.4)
Nonserious TEAE	6 (4.2)	4 (2.9)	6 (3.5)	5 (3.3)	19 (5.7)	6 (14.6)
Mild TEAEs	4 (2.8)	3 (2.1)	4 (2.4)	4 (2.6)	14 (4.2)	1 (2.4)
Moderate TEAEs	4 (2.8)	2 (1.4)	4 (2.4)	2 (1.3)	16 (4.8)	5 (12.2)
Severe TEAEs	0	0	0	0	0	1 (2.4)
Serious TEAEs	2 (1.4)	1 (0.7)	2 (1.2)	1 (0.7)	9 (2.7)	3 (7.3)
Fatal TEAEs	0	0	0	0	0	0
TEAEs Leading to Discontinuation of IP	0	0	0	0	0	0
TEAEs Related to IP	1 (0.7)	0	1 (0.6)	0	1 (0.3)	0
History of Supraventricular Tachyarrhythmia	5 (3.5)	3 (2.1)	5 (2.9)	4 (2.6)	13 (3.9)	2 (4.9)
Concurrent Decreased LVEF < 50%	0	0	0	0	0	2 (4.9)
Event Started After EOT	0	0	0	1 (0.7)	0	1 (2.4)
Onset Latency (Days)	9-168	27-176	9-168	27-176	1-672	54-589

CMQ = customized MedDRA query; EOT = end of treatment; IP = investigational product; LVEF = left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; TEAE = treatment-emergent adverse event

Dizziness

Dizziness was evaluated through a CMQ that included PTs denoting dizziness (dizziness, dizziness postural, vertigo, presyncope, balance disorder, vertigo positional).

Pivotal phase 3 study (CY 6031)

The incidence of dizziness TEAEs in CY 6031 was low and balanced between the treatment groups (7 participants [4.9%] in the aficamten group and 6 participants [4.3%] in the placebo group).

Integrated safety analysis – Pools 1 and 2

In Pool 1, the incidence of dizziness TEAEs was modestly higher in the aficamten group than the placebo group (13 participants [7.6%] aficamten, 7 participants [4.6%] placebo); the higher incidence was mainly driven by the PT of dizziness (Table). Dizziness was considered by the investigator as related to IP for 1 participant (0.6%) in the aficamten group and 3 participants (2.0%) in the placebo group. The 1 related case in the aficamten group was mild in severity and resolved with no change in aficamten dose. The onset of dizziness TEAEs was widely variable and not different between the aficamten group (4 to 170 days) and the placebo group (2 to 168 days), and most occurred while the participant was on treatment (11 participants [6.5%] aficamten, 7 participants [4.6%] placebo). All TEAEs of dizziness were mild or moderate in severity and nonserious.

In Pool 2, a dizziness event was reported for 42 participants (12.5%) (Table). The most frequent events were TEAEs of dizziness (8.7%) and vertigo (2.4%). Dizziness events were severe for 1 participant (0.3%) and serious for 1 participant (0.3%). No dizziness event led to discontinuation of IP. Most TEAEs of dizziness were nonserious (1 case of positional vertigo reported in CY 6022 was serious). Most were mild or moderate, did not result in aficamten dose change, and most resolved despite continuation of treatment. arrhythmia.

Across all pools, no dizziness TEAE led to discontinuation of IP, and no participant with a dizziness TEAE had concurrent hypotension. Few participants reporting a dizziness TEAE had history of dizziness or arrhythmia (Table).

Table 56: Treatment-emergent Dizziness Events (Safety Analysis Set) (Source: Table 24, Summary of Clinical Safety).

Dizziness CMQ Preferred Term	CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N = 142)	Placebo (N = 140)	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 335)	Aficamten (N = 41)
Participants With Any TEAE	7 (4.9)	6 (4.3)	13 (7.6)	7 (4.6)	42 (12.5)	8 (19.5)
EAIR (persons per 100 person-years)	9.54	9.76	16.23	10.67	10.45	14.36
Balance Disorder	0	0	0	0	3 (0.9)	0
Dizziness	6 (4.2)	2 (1.4)	11 (6.5)	3 (2.0)	29 (8.7)	8 (19.5)
Dizziness Postural	0	1 (0.7)	1 (0.6)	1 (0.7)	4 (1.2)	0
Presyncope	0	1 (0.7)	0	1 (0.7)	2 (0.6)	0
Vertigo	1 (0.7)	4 (2.9)	1 (0.6)	4 (2.6)	8 (2.4)	0
Vertigo Positional	0	0	0	0	2 (0.6)	0
Nonserious TEAE	7 (4.9)	6 (4.3)	13 (7.6)	7 (4.6)	42 (12.5)	8 (19.5)
Mild TEAEs	7 (4.9)	6 (4.3)	12 (7.1)	7 (4.6)	37 (11.0)	6 (14.6)
Moderate TEAEs	0	1 (0.7)	1 (0.6)	1 (0.7)	9 (2.7)	2 (4.9)
Severe TEAEs	0	0	0	0	1 (0.3)	0
Serious TEAEs	0	0	0	0	1 (0.3)	0
TEAEs Leading to Discontinuation of IP	0	0	0	0	0	0
TEAEs Related to IP	1 (0.7)	2 (1.4)	1 (0.6)	3 (2.0)	7 (2.1)	2 (4.9)
Concurrent Arrhythmias	0	0	0	0	1 (0.3)	0
Concurrent Hypotension	0	0	0	0	0	0
History of Dizziness	1 (0.7)	0	3 (1.8)	0	9 (2.7)	1 (2.4)
History of Arrhythmias	1 (0.7)	2 (1.4)	5 (2.9)	2 (1.3)	19 (5.7)	4 (9.8)
Dizziness Event Started After EOT	1 (0.7)	0	3 (1.8)	0	3 (0.9)	0
Onset Latency (Days)	4-170	2-168	4-170	2-168	4-994	1-688

CMQ = customized MedDRA query; CNS = central nervous system; EAIR = exposure-adjusted incidence rate; EOT = end of treatment; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; PT = preferred term; TEAE = treatment-emergent adverse event.

Syncope

Pivotal phase 3 study (CY 6031)

The incidence of syncope TEAEs in CY 6031 was low in the treatment groups (2 participants [1.4%] in the aficamten group and 4 participants [2.9%] in the placebo group).

Integrated safety analysis – Pools 1 and 2

A CMQ of syncope included the PTs of syncope, presyncope, and loss of consciousness.

In Pool 1, the participant incidence of a syncope event was low (3 participants [1.8%] aficamten, 5 participants [3.3%] placebo) (Table). In the aficamten group, no event was severe, serious, or led to discontinuation of IP, whereas in the placebo group, syncope events were both severe and serious in 3 participants (2.0%) and led to discontinuation of IP for 1 participant (0.7%).

In Pool 2, with increased aficamten exposure, the participant incidence of syncope (2.1%) remained similar to that of Pool 1.

No event of syncope across any of the pools led to dose interruption.

Table 57: Treatment-emergent Syncope Events (Safety Analysis Set) (Source: Table 25, Summary of Clinical Safety).

Syncope CMQ Preferred Term	CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N = 142)	Placebo (N = 140)	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 335)	Aficamten (N = 41)
Participants With Any TEAE	2 (1.4)	4 (2.9)	3 (1.8)	5 (3.3)	9 (2.7)	1 (2.4)
EAIR (persons per 100 person-years)	2.66	5.42	3.64	6.47	2.07	1.55
Loss of Consciousness	0	1 (0.7)	0	1 (0.7)	0	1 (2.4)
Presyncope	0	1 (0.7)	0	1 (0.7)	2 (0.6)	0
Syncope	2 (1.4)	2 (1.4)	3 (1.8)	3 (2.0)	7 (2.1)	1 (2.4)
Nonserious TEAE	2 (1.4)	2 (1.4)	3 (1.8)	3 (2.0)	7 (2.1)	1 (2.4)
Mild TEAEs	2 (1.4)	1 (0.7)	3 (1.8)	1 (0.7)	5 (1.5)	0
Moderate TEAEs	0	1 (0.7)	0	2 (1.3)	3 (0.9)	1 (2.4)
Severe TEAEs	0	2 (1.4)	0	3 (2.0)	1 (0.3)	0
Serious TEAEs	0	2 (1.4)	0	3 (2.0)	2 (0.6)	0
Fatal TEAEs	0	0	0	0	0	0
TEAEs Leading to Discontinuation of IP	0	1 (0.7)	0	1 (0.7)	0	0
TEAEs Related to IP	0	0	0	0	0	1 (2.4)
Concurrent Arrhythmias	0	0	0	0	0	0
Concurrent Hypotension	0	0	0	1 (0.7)	0	0
History of Syncope	0	2 (1.4)	0	2 (1.3)	0	1 (2.4)
History of Arrhythmias	0	2 (1.4)	0	3 (2.0)	1 (0.3)	1 (2.4)
Syncope Event Started After EOT	0	0	0	1 (0.7)	0	0
Onset Latency (Days)	59-162	29-170	10-162	29-170	10-907	178-244

CMQ = customized MedDRA query; EAIR = exposure-adjusted incidence rate; EOT = end of treatment; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; TEAE = treatment-emergent adverse event.

Stroke

Integrated safety analysis – Pools 1 and 2

Events of stroke were evaluated using narrow SMQs of Ischemic central nervous system vascular conditions and Haemorrhagic central nervous system vascular conditions (Table). Overall, stroke TEAEs were reported in few participants across all pools.

In Pool 1, a stroke event was reported for 1 participant in each of the aficamten and placebo groups. The participant in the aficamten group had carotid artery stenosis and ischemic stroke; both events were severe and serious. Neither event led to interruption of IP or discontinuation of IP.

In Pool 2, 6 participants (1.8%), including the aficamten-treated participant described in Pool 1, had at least 1 stroke event; the event was serious for all the participants. No event led to discontinuation of IP.

In Pool 3, 1 participant had a severe, serious stroke event that did not lead to discontinuation of IP.

Across all pools, no event of stroke was fatal or considered related to treatment.

Table 58: Treatment-emergent Stroke Events (Safety Analysis Set) (Source: Table 26, Summary of Clinical Safety).

	CY 6031		Pool 1		Pool 2	Pool 3
Stroke CMQ[a] Preferred Term	Aficamten (N = 142)	Placebo (N = 140)	Aficamten (N = 170)	Placebo (N = 153)	Aficamten (N = 335)	Aficamten (N = 41)
Participants With Any TEAE	1 (0.7)	1 (0.7)	1 (0.6)	1 (0.7)	6 (1.8)	1 (2.4)
EAIR (persons per 100 person-years)	1.32	1.34	1.20	1.28	1.38	1.55
Carotid Artery Stenosis	1 (0.7)	0	1 (0.6)	0	2 (0.6)	0
Cerebral Ischaemia	0	1 (0.7)	0	1 (0.7)	0	0
Embolic Stroke	0	0	0	0	2 (0.6)	1 (2.4)
Ischaemic Stroke	1 (0.7)	0	1 (0.6)	0	1 (0.3)	0
Middle cerebral artery stroke	0	0	0	0	1 (0.3)	0
Subdural haematoma[b]	0	0	0	0	1 (0.3)	0
Subdural haemorrhage[b]	0	0	0	0	1 (0.3)	0
Nonserious TEAE	0	1 (0.7)	0	1 (0.7)	1 (0.3)	0
Mild TEAEs	0	0	0	0	1 (0.3)	0
Moderate TEAEs	0	1 (0.7)	0	1 (0.7)	2 (0.6)	0
Severe TEAEs	1 (0.7)	0	1 (0.6)	0	3 (0.9)	1 (2.4)
Serious TEAEs	1 (0.7)	0	1 (0.6)	0	6 (1.8)	1 (2.4)
Fatal TEAEs	0	0	0	0	0	0
TEAEs Leading to Discontinuation of IP	0	0	0	0	0	0
TEAEs Related to IP	0	0	0	0	0	0
Concurrent Arrhythmias	0	0	0	0	0	0
History of Stroke	0	0	0	0	0	0
History of Arrhythmias	0	0	0	0	2 (0.6)	1 (2.4)
Stroke Event Started After EOT	1 (0.7)	0	1 (0.6)	0	1 (0.3)	0
Onset Latency (Days)	171-171	137-137	171-171	137-137	67-473	146-146

EAIR = exposure-adjusted incidence rate; EOT = end of treatment; IP = investigational product; N = number of participants; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event. [a] Stroke was defined through narrow SMQs of Ischemic central nervous system vascular conditions and Hemorrhagic central nervous system vascular conditions. [b] Subdural hematoma and subdural hemorrhage (reported for 1 participant each) were both associated with a mechanical fall.

Renal Events

Integrated safety analysis – Pools 1 and 2

Renal events were summarized using 2 SMQs (Acute renal failure and Chronic kidney disease) to assess the potential of aficamten for renal toxicity.

In Pool 1, acute renal failure TEAEs (broad SMQ) were reported for 2 participants (1.2%) in the aficamten group and 2 participants (1.3%) in the placebo group; TEAEs of chronic kidney disease (broad SMQ) were reported for 2 participants (1.2%) in the aficamten group and 5 participants (3.3%) in the placebo group. All events were mild or moderate in severity; no event was serious and no event led to either interruption of IP or discontinuation of IP.

In Pool 2, TEAEs of acute renal failure (broad SMQ) were reported for 6 participants (1.8%), and TEAEs of chronic kidney disease were reported for 12 participants (3.6%). All renal events were mild or moderate in severity, nonserious, and no event led to either interruption of IP or discontinuation of IP.

Renal Failure Events Preferred Term	Pool 1		Pool 2	Pool 3
	Aficamten (N = 170) n (%)	Placebo (N = 153) n (%)	Aficamten (N = 335) n (%)	Aficamten (N = 41) n (%)
Acute Renal Failure SMQB	2 (1.2)	2 (1.3)	6 (1.8)	0
EAIR (persons per 100 person-years)	2.42	2.58	1.37	0
Acute Kidney Injury	1 (0.6)	0	2 (0.6)	0
Blood Creatinine Increased	0	0	1 (0.3)	0
Blood Urea Increased	1 (0.6)	0	1 (0.3)	0
Glomerular Filtration Rate Decreased	0	0	1 (0.3)	0
Protein Urine Present	0	1 (0.7)	0	0
Proteinuria	0	1 (0.7)	0	0
Renal Failure	0	0	1 (0.3)	0
Acute Renal Failure SMQN	1 (0.6)	0	3 (0.9)	0
EAIR (persons per 100 person-years	1.20	0	0.68	0
Acute Kidney Injury	1 (0.6)	0	2 (0.6)	0
Renal Failure	0	0	1 (0.3)	0
Chronic Kidney Disease SMQB	2 (1.2)	5 (3.3)	12 (3.6)	0
EAIR (persons per 100 person-years)	2.43	6.50	2.76	0
Blood Potassium Increased	1 (0.6)	1 (0.7)	3 (0.9)	0
Blood Urea Increased	1 (0.6)	0	1 (0.3)	0
Hyperparathyroidism	0	0	2 (0.6)	0
Pericarditis	0	0	2 (0.6)	0
Blood Creatinine Increased	0	0	1 (0.3)	0
Glomerular Filtration Rate Decreased	0	0	1 (0.3)	0
Hyperkalemia	1 (0.6)	0	1 (0.3)	0
Hypervolemia	1 (0.6)	0	0	0
Hyponatremia	0	2 (1.3)	0	0
Microalbuminuria	0	0	1 (0.3)	0
Protein Urine Present	0	1 (0.7)	0	0
Proteinuria	0	1 (0.7)	0	0
Renal Failure	0	0	1 (0.3)	0

EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SMQB = standardized MedDRA query broad; SMQN = standardized MedDRA query narrow.

Hepatic Events

Integrated safety analysis – Pools 1 and 2

Potential hepatic effects were evaluated using broad SMQ Drug-related hepatic disorders - comprehensive search. Results are summarized in Table .

In Pool 1, hepatic events were reported for 2 participants (1.2%) in the aficamten group and 2 participants (1.3%) in the placebo group. All events were mild or moderate in severity; all were nonserious, and none led to either IP interruption or discontinuation.

In Pool 2, hepatic events were reported for 9 participants (2.7%); those reported for > 1 participant were hepatic steatosis (3 participants [0.9%] and INR increased (2 participants [0.7%]h). All hepatic events were mild or moderate in severity, nonserious, and none led to either interruption or discontinuation of IP.

Additional details of participants with elevated liver enzymes are provided in Section on laboratory findings below. No participant met Hy's law criteria.

Table 59: Hepatic Events of Interest (Safety Analysis Set) (Source: Table 28, Summary of Clinical Safety).

Drug-related Hepatic Disorders – Comprehensive Search SMQB Preferred Term	Pool 1		Pool 2	Pool 3
	Aficamten (N = 170) n (%)	Placebo (N = 153) n (%)	Aficamten (N = 335) n (%)	Aficamten (N = 41) n (%)
Participants With Any TEAE	2 (1.2)	2 (1.3)	9 (2.7)	0
EAIR (persons per 100 person-years	2.43	2.58	2.10	0
Hepatic Cytolysis	1 (0.6)	0	1 (0.3)	0
International Normalized Ratio Increased	1 (0.6)	0	2 (0.6)	0
Hepatic Steatosis	0	1 (0.7)	3 (0.9)	0
Non-alcoholic Fatty Liver	0	1 (0.7)	1 (0.3)	0
ALT Increased	0	0	1 (0.3)	0
Blood Bilirubin Increased	0	0	1 (0.3)	0
GGT Increased	0	0	1 (0.3)	0
Hyperbilirubinemia	0	0	1 (0.3)	0
Prothrombin Time Prolonged	0	0	1 (0.3)	0
Serious TEAE	0	0	0	0
Mild TEAE	1 (0.6)	2 (1.3)	6 (1.8)	0
Moderate TEAE	1 (0.6)	0	3 (0.9)	0
Severe TEAE	0	0	0	0
TEAEs Related to IP	0	0	1 (0.3)	0
TEAE Leading to Dose Interruption	0	0	0	0
TEAE Leading to Permanent Discontinuation of IP	0	0	0	0
TEAE Leading to Death	0	0	0	0
History of Drug-related Hepatic Disorder	15 (8.8)	11 (7.2)	26 (7.8)	4 (9.8)

ALT = alanine aminotransferase; EAIR = exposure-adjusted incidence rate; GGT = gamma-glutamyl transferase; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SMQB = standardized MedDRA query broad; TEAE = treatment-emergent adverse event.

Potential Adverse Drug Reactions

Potential ADRs were defined as TEAEs that occurred in ≥ 5% of participants in CY 6031 and occurred in the aficamten group at least 2% more frequently (absolute difference) than in the placebo group. Based on these criteria, hypertension and palpitations qualified as potential ADRs.

Due to the mechanism of action and expected pharmacodynamic effect of aficamten, the profile of LVEF has been thoroughly evaluated and are described below. Based on this review, systolic dysfunction, defined as LVEF < 50% with or without symptoms, is proposed as an adverse drug reaction. LVEF < 50% was observed at an incidence of 3.5% in the aficamten group in the pivotal clinical trial CY 6031.

Hypertension

Pivotal phase 3 trial (CY 6031)

In this study a greater proportion of participants in the aficamten group had a TEAE of hypertension than in the placebo group: 11 participants (7.7%) compared with 3 participants (2.1%), respectively. Overall, all TEAEs were reported as non-serious, mild, or moderate and none led to discontinuation of the IP. Of note, among the 11 participants in the aficamten group with a TEAE of hypertension, 8 had a history of hypertension.

In the aficamten group, the majority of TEAEs of hypertension were mild (as reported for 8 of 11 participants), assessed as not related to the IP by the investigator (for 9 of 11 participants) and resolved (for 7 of 11 participants) while aficamten was ongoing at unchanged dose. There was no apparent pattern of event onset latency relative to aficamten treatment initiation: time to onset ranged from 36 to 173 days. This imbalance triggered an in-depth post hoc analysis. An overview of TEAEs denoting hypertension is presented in Table .

Integrated safety analysis – Pools 1 and 2

The proportion of participants with hypertension in Pool 1 reflected that observed in CY 6031. Events of hypertension were primarily reported during the treatment period, with no participant in the aficamten group and 2 participants (1.3%) in the placebo group having TEAEs of hypertension during the washout period. In Pool 2, the incidence of hypertension in participants with a longer duration of exposure to aficamten remained unchanged (32 participants [9.6%]). In participants with nHCM (Pool 3), 6 participants (14.6%) had TEAEs of hypertension.

Overall, except for 1 serious and severe event of hypertensive urgency in a participant with oHCM in CY 6022, all events of hypertension recorded in CY 6031, CY 6022, and CY 6021 were mild to moderate in severity and nonserious (Table). No TEAE of hypertension resulted in discontinuation of IP. There was no apparent pattern of event onset latency relative to aficamten treatment initiation: the time to onset ranged from 15 to 741 days.

Consistent with observed differences in incidence rates of hypertension TEAEs, small mean increases in both systolic and diastolic BP were observed in the aficamten group but not in the placebo group. This is further described in Section Vital Signs.

Table 60: Treatment-emergent Adverse Event of Interest: Hypertension SMQB. (Source: Table 16, Summary of Clinical Safety).

	CY 6031		Pool 1		Pool 2	Pool 3
Participants, n (%), With:	**Aficamten (N = 142) n (%)**	**Placebo (N = 140) n (%)**	**Aficamten (N = 170) n (%)**	**Placebo (N = 153) n (%)**	**Aficamten (N = 335) n (%)**	**Aficamten (N = 41) n (%)**
Any TEAE of Hypertension	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	32 (9.6)	6 (14.6)
EAIR (persons per 100 person years)	15.24	4.08	13.78	5.19	7.86	10.08
BP Increased	0	0	0	0	3 (0.9)	1 (2.4)
BP Systolic Increased	0	0	0	0	1 (0.3)	0
Diastolic Hypertension	0	0	0	0	1 (0.3)	0
Hypertension	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	27 (8.1)	4 (9.8)
Hypertensive Emergency	0	0	0	0	0	1 (2.4)
Hypertensive Urgency	0	0	0	0	2 (0.6)	0
Nonserious TEAE	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	32 (9.6)	6 (14.6)
Mild/Moderate TEAEs	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	31 (9.3)	6 (14.6)
Severe TEAEs	0	0	0	0	1 (0.3)	0
Serious TEAEs	0	0	0	0	1 (0.3)	0
Fatal TEAEs	0	0	0	0	0	0
TEAE Leading to Discontinuation of IP	0	0	0	0	0	0
TEAEs Reported as Related to IP	2 (1.4)	1 (0.7)	2 (1.2)	1 (0.7)	2 (0.6)	0
History of Hypertension	8 (5.6)	3 (2.1)	8 (4.7)	4 (2.6)	22 (6.6)	6 (14.6)
Onset Latency (days)	15-173	29-176	15-173	29-176	15-993	16-526

Participants, n (%), With:	CY 6031		Pool 1		Pool 2	Pool 3
	Aficamten (N = 142) n (%)	Placebo (N = 140) n (%)	Aficamten (N = 170) n (%)	Placebo (N = 153) n (%)	Aficamten (N = 335) n (%)	Aficamten (N = 41) n (%)
Any TEAE of Hypertension	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	32 (9.6)	6 (14.6)
EAIR (persons per 100 person years)	15.24	4.08	13.78	5.19	7.86	10.08
BP Increased	0	0	0	0	3 (0.9)	1 (2.4)
BP Systolic Increased	0	0	0	0	1 (0.3)	0
Diastolic Hypertension	0	0	0	0	1 (0.3)	0
Hypertension	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	27 (8.1)	4 (9.8)
Hypertensive Emergency	0	0	0	0	0	1 (2.4)
Hypertensive Urgency	0	0	0	0	2 (0.6)	0
Nonserious TEAE	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	32 (9.6)	6 (14.6)
Mild/Moderate TEAEs	11 (7.7)	3 (2.1)	11 (6.5)	4 (2.6)	31 (9.3)	6 (14.6)
Severe TEAEs	0	0	0	0	1 (0.3)	0
Serious TEAEs	0	0	0	0	1 (0.3)	0
Fatal TEAEs	0	0	0	0	0	0
TEAE Leading to Discontinuation of IP	0	0	0	0	0	0
TEAEs Reported as Related to IP	2 (1.4)	1 (0.7)	2 (1.2)	1 (0.7)	2 (0.6)	0
History of Hypertension	8 (5.6)	3 (2.1)	8 (4.7)	4 (2.6)	22 (6.6)	6 (14.6)
Onset Latency (days)	15-173	29-176	15-173	29-176	15-993	16-526

AE = adverse event; BP = blood pressure; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; N = number of participants; PT = preferred term; SMQB = standardized MedDRA query broad; TEAE = treatment-emergent adverse event. TEAEs are adverse events that started or worsened in the treatment-emergent period (ie, from the first dose date to the last dose date + 30 [CY 6021] or 28 [CY 6031, CY 6022] days). Last dose date is as reported for participants who completed or discontinued the study, or the data cutoff date for ongoing participants. Adverse events were coded per MedDRA version 26.0 for CY 6031 and Pool 1 and version 27.0 for Pool 2 and Pool 3. Participants with multiple events coded to the same TEAE of interest/PT were counted only once for the TEAE of interest/PT. Onset latency presents the range of AE onset relative to the first dose date in the study/pool.

Palpitations

Pivotal phase 3 study (CY6031)

An imbalance of reported TEAEs of palpitations was observed in CY 6031 (7.0% aficamten, 2.9% placebo) (Table). All events of palpitation were either mild or moderate in severity; none was severe, serious, fatal, or led to discontinuation of IP. All events in the aficamten group were assessed by the investigators as not related to IP. There was no apparent pattern of event onset latency relative to initiation of aficamten treatment (ranging from 4 to 360 days), and the frequency of events did not increase with increased exposure duration, as reflected in Pool 2 (Table). A small number of

participants had a history of palpitations while other participants had relevant history such as arrhythmias, cardiac ischemia, anxiety, hypertension, and diabetes.

Integrated safety analysis – Pools 1 and 2

In Pool 1, there were no new events; all events of palpitations had occurred in CY 6031. In Pool 2, palpitations were reported for 8.7% of participants. Two participants (0.6%) had events assessed by the investigators as related to IP. There was no apparent pattern of event onset latency relative to initiation of aficamten treatment (ranging from 4 to 860 days) (Table). The incidence of palpitations did not increase with in increased exposure duration in Pool 2: the EAIR for palpitations in aficamten-treated participants in Pool 1 was 12.46 persons per 100 person-years; in comparison, the EAIR in Pool 2 was 6.91 persons per 100 person-years (Table). A small number of participants had a history of palpitations while other participants had relevant history such as arrhythmias, cardiac ischemia, anxiety, hypertension, and diabetes.

Table 61: Treatment-emergent Adverse Event of Interest: Palpitations PT (Source: Table 17, Summary of Clinical Safety).

	CY 6031		Pool 1		Pool 2	Pool 3
Participants, n (%), With:	**Aficamten (N = 142) n (%)**	**Placebo (N = 140) n (%)**	**Aficamten (N = 170) n (%)**	**Placebo (N = 153) n (%)**	**Aficamten (N = 335) n (%)**	**Aficamten (N = 41) n (%)**
Any TEAE of Palpitations	10 (7.0)	4 (2.9)	10 (5.9)	5 (3.3)	29 (8.7)	5 (12.2)
EAIR (persons per 100 person years)	13.76	5.44	12.46	6.51	6.91	8.56
Palpitations	10 (7.0)	4 (2.9)	10 (5.9)	5 (3.3)	29 (8.7)	5 (12.2)
Nonserious TEAE	10 (7.0)	4 (2.9)	10 (5.9)	5 (3.3)	29 (8.7)	5 (12.2)
Mild/Moderate TEAEs	10 (7.0)	4 (2.9)	10 (5.9)	5 (3.3)	29 (8.7)	5 (12.2)
Severe TEAEs	0	0	0	0	0	0
Serious TEAEs	0	0	0	0	0	0
Fatal TEAEs	0	0	0	0	0	0
TEAE Leading to Discontinuation of IP	0	0	0	0	0	0
TEAEs Reported as Related to IP	0	1 (0.7)	0	2 (1.3)	2 (0.6)	0
Concurrent Arrhythmia	1 (0.7)	0	1 (0.6)	0	1 (0.3)	1 (2.4)
History of Palpitations	1 (0.7)	2 (1.4)	1 (0.6)	2 (1.3)	2 (0.6)	1 (2.4)
History of Arrhythmias	3 (2.1)	1 (0.7)	3 (1.8)	1 (0.7)	9 (2.7)	2 (4.9)
Palpitation Event Started After EOT	2 (1.4)	2 (1.4)	2 (1.2)	2 (1.3)	2 (0.6)	1 (2.4)
Onset Latency (days)	4-202	50-178	4-202	33-178	4-860	17-615

AE = adverse event; EOI = event of interest; EOT = end of treatment; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; N = number of participants; PT = preferred term; TEAE = treatment emergent adverse event. TEAEs are adverse events that started or worsened in the treatment-emergent period (ie, from the first dose date to the last dose date + 30 [CY 6021] or 28 [CY 6031, CY 6022] days). Last dose date is as reported for participants who completed or discontinued the study, or the data cutoff date for ongoing participants. Adverse events were coded per MedDRA version 26.0 for CY 6031 and Pool 1 and version 27.0 for Pool 2 and Pool 3. Participants with multiple events coded to the same EOI/PT were counted only once for the EOI/PT.

Left Ventricular Ejection Fraction

Pivotal phase 3 trial (CY 6031)

Core Laboratory-Assessed LVEF

Mean LVEF values as assessed by the core laboratory and changes from baseline are summarized in Table ; mean values (± SD) during the study are depicted in Figure .

Table 62: Change from Baseline in Core Laboratory-Assessed LVEF (Source: Table 49, CY 6031, Clinical Study Report).

Core Laboratory-Assessed LVEF (%)	Aficamten (N=142)	Placebo (N=140)
Baseline		
n	142	140
Mean (SD)	74.80 (5.480)	74.76 (6.255)
Min, Max	56.2, 87.4	51.1, 86.9
Week 8		
n	129	130
Mean (SD)	70.69 (7.451)	74.22 (5.880)
Min, Max	39.2, 86.4	49.6, 84.6
LS mean change from baseline (SE)	−3.91 (0.487)	−0.50 (0.487)
LS mean difference vs placebo (95% CI), p-value	−3.41 (−4.76, −2.07) p < 0.0001	
Week 24		
n	134	133
Mean (SD)	67.91 (7.427)	72.81 (6.542)
Min, Max	45.5, 85.7	53.5, 85.8
LS mean change from baseline (SE)	−6.77 (0.551)	−2.02 (0.553)
LS mean difference vs placebo (95% CI), p-value	−4.75 (−6.27, −3.22) p < 0.0001	
Week 28		
n	136	131
Mean (SD)	71.17 (5.978)	72.03 (6.233)
Min, Max	50.1, 83.9	53.8, 85.7
LS mean change from baseline (SE)	−3.65 (0.459)	−2.83 (0.468)
LS mean difference vs placebo (95% CI), p-value	−0.82 (−2.09, 0.45) p = 0.206	

CI = confidence interval; LS = least squares; LVEF = left ventricular ejection fraction; SD = standard deviation; SE = standard error. Notes: Data up to Week 24 were analysed using a mixed model for repeated measures with baseline as covariate, randomization stratification factors, visit, treatment group, and interaction terms of treatment by visit and baseline by visit. An unstructured covariance matrix was specified. Week 28 data were analysed using an analysis of covariance model with baseline as covariate, randomization stratification factors and treatment group as fixed effects.

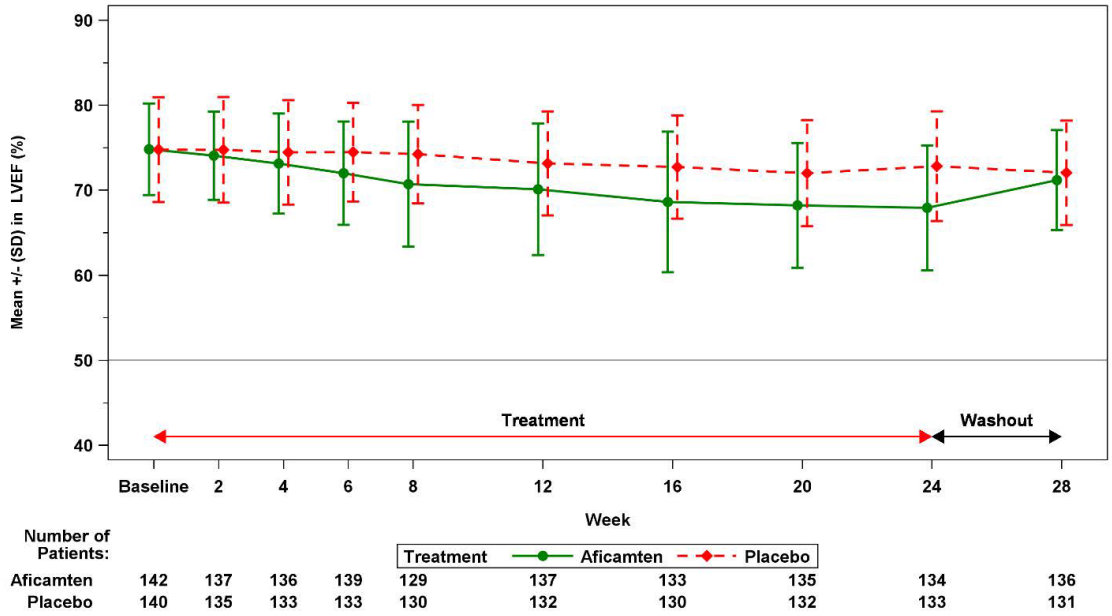


Figure 29: Mean LVEF from Baseline Over Time (Full Analysis Set) (Source: Figure 11, CY 6031, Clinical Study Report).

Table 5063: Participants with LVEF < 50% per Core Laboratory Assessment of Echocardiography (Source: Table 50, CY 6031, Clinical Study Report).

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Signs/Symptoms of Heart Failure[a]
Aficamten dose (mg QD)	NA	5	10	15	20	20	20	20	20	NA	None
LVEF core lab (%)	65.2	66.1	64.5	62.9	47.8	56.3	66.4	66.5	65.4	70.5	
LVEF site (%)	56	62	60	62	62	65	59	64	66	–	
Postdose aficamten plasma concentration (ng/mL)	BLQ	75.7	187	295	336	394	368	381	320	NA	
Aficamten dose (mg QD)	NA	5	5	5	5	5	5	5	5	NA	None
LVEF core lab (%)	56.2	46.5	47.1	51.3	47.1	48.7	54.5	51.8	45.5	50.9	
LVEF site (%)	65	60	56	55	55	60	60	60	60	–	
Postdose aficamten plasma concentration (ng/mL)	BLQ	192	227	219	219	192	196	177	203	NA	
Aficamten dose (mg QD)	NA	5	10	15	15	15	15	10	10	NA	None
LVEF core lab (%)	63.1	72.9	58.8	49.7	39.2	44.3	33.9	55.2	54.8	50.1	
LVEF site (%)	65	61	68	54	57	54	49	51	47	–	
Postdose aficamten plasma concentration (ng/mL)	BLQ	95.3	182	330	287	334	382	227	Missing	NA	

Table 63: Participants with LVEF < 50% per Core Laboratory Assessment of Echocardiography (Continued)

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Signs/Symptoms of Heart Failure[a]
Aficamten dose (mg QD)	NA	5	10	15	15	15	15	15	15	NA	None
LVEF core lab (%)	79.8	75.8	77.1	60.9	74.8	75.1, 67.1	51.7	47.7	51.6	68.3	
LVEF site (%)	56	60	65	60	60	63, 60	60	52	51	–	
Postdose aficamten plasma concentration (ng/mL)	BLQ	96.1	256	350	397	379	396	435	368	NA	
Aficamten dose (mg QD)	NA	5	10	15	20	20	20	20	20	NA	None
LVEF core lab (%)	84	76	67.6	68.4	60.8	68.7	42.8	72.2	59.2	74.8	
LVEF site (%)	79	74	77	68	57	75	59	68	70	–	
Postdose aficamten plasma concentration (ng/mL)	BLQ	117	232	364	483	495	712	530	471	NA	
Placebo	NA	placebo	placebo	placebo	placebo	placebo	placebo	placebo	placebo	NA	Peripheral edema
LVEF core lab (%)	53	56.2	60.1	48.4	49.6	52.6	56.7	52.3	56.2	59.4	
LVEF site (%)	62	56	46	45	51	46	45	60	56	–	
Postdose aficamten plasma concentration (ng/mL)	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	NA	

BLQ = below the limit of quantitation (< 1 ng/mL); LVEF = left ventricular ejection fraction; NA = not applicable; QD = once daily

[a] Signs and symptoms of heart failure were based on a custom preferred terms search and occurred within 7 days from the time when LVEF was < 50%.

Site-Assessed LVEF

In total, 8 participants (7 aficamten [4.9%], 1 placebo [0.7%]) had at least 1 site-assessed- LVEF value < 50%. Two of these participants (a participant in the aficamten group and a participant in the placebo group) also had core laboratory LVEF values < 50%, as shown in Table . Case profiles, including LVEF, aficamten dose, and plasma concentration, for each of the remaining 6 participants are summarized in Table . Plasma concentrations for nearly all participants remained relatively stable at the time of the occurrence of LVEF < 50%, and there were no substantial excursions associated with large decreases of LVEF < 50%.

Following the site-assessed findings, all 7 aficamten-treated participants had a subsequent dose reduction (per protocol), and all participants had an LVEF ≥ 50% at the next visit. There were no treatment interruptions due to LVEF < 50% and no associated signs or symptoms of heart failure.

Table 5164: Participants with LVEF < 50% per Site Assessment of Echocardiograph (Source: Table 51, CY 6031, Clinical Study Report).

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Signs/Symptoms of Heart Failure[a]
Aficamten dose (mg QD)	NA	5	10	15	20	20	20	15	15	NA	None
LVEF site (%)	63	60	60	67	64	63	46	50	58	-	
LVEF core lab (%)	68.5	74.1	73.6	73.8	68.2	64.1	51.1	60.3	66.7	72.6-	
Postdose aficamten plasma concentration (ng/mL)	BLQ	129	227	404	598	635	620	448	391	NA	
Aficamten dose (mg QD)	NA	5	10	15	15	15	10	10	10	NA	None
LVEF site (%)	70	70	70	60	57	48	52	55	52	-	
LVEF core lab (%)	77.1	75.7	71.5	59.1	-	69.9	-	59.7	68.6	72.6	
Postdose aficamten plasma concentration (ng/mL)	BLQ	90.7	192	261	285	296	172	204	189	NA	
Aficamten dose (mg QD)	NA	5	10	15	15	15	15	10	10	NA	None
LVEF site (%)	70	63	64	58	50	50	48	50	52	-	
LVEF core lab (%)	87.4	83.7	83.6	80.8	79.8	76.4	53.3	51.8	59.1	75.2	
Postdose aficamten plasma concentration (ng/mL)	BLQ	182	486	862	945	1060	1230	775	658	NA	

Table: Participants with LVEF < 50% per Site Assessment of Echocardiograph (Continued)

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Signs/Symptoms of Heart Failure[a]

	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Signs/Symptoms of Heart Failure[a]
Aficamten dose (mg QD)	NA	5	10	15	20	20	20	15	15	NA	None
LVEF site (%)	66	61	62	66	65	55	47	50	55	-	
LVEF core lab (%)	69.9	69.7	70.8	65.2	63.8	61.8	58.5	53.8	50.2	62.7	
Postdose aficamten plasma concentration (ng/mL)	BLQ	92.9	144	211	289	301	282	246	214	NA	
Aficamten dose (mg QD)	NA	5	10	15	15	10	10	10	10	NA	None
LVEF site (%)	71	56	57	50	49	54	60	61	58	-	
LVEF core lab (%)	76.3	72.5	72.4	72.2	72.2	60.1	73.1	66.4	75.4	77.1	
Postdose aficamten plasma concentration (ng/mL)	BLQ	151	257	404	393	309	277	318	256	NA	
Aficamten dose (mg QD)	NA	5	10	15	20	20	20	20	15	NA	None
LVEF site (%)	67	65	65	60	65	60	65	45	60	-	
LVEF core lab (%)	76.3	77.1	70.2	57	67.1	-	-	53	61.4	62.9	
Postdose aficamten plasma concentration (ng/mL)	BLQ	94.2	192	234	362	346	392	338	272	NA	

BLQ = below the limit of quantitation (< 1 ng/mL); LVEF = left ventricular ejection fraction; NA = not applicable; QD = once daily

[a] Signs and symptoms of heart failure were based on a custom preferred terms search and occurred within 7 days from the time when LVEF was < 50

Integrated safety analysis – Pools 1 and 2

Participants With oHCM

In Pool 1 (170 participants treated with aficamten, 153 participants treated with placebo), 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. Small mean decreases from baseline in the aficamten group compared with placebo were observed during the treatment period, with mean changes of −4.0 versus −0.5%, respectively, at Week 8 after completion of dose titration and −6.8 versus −2.1%, respectively, at Week 24 at the end of treatment. The mean difference in LVEF between the aficamten and placebo groups was negligible after the 4-week washout period.

Per the core laboratory assessment in Pool 1, 7 participants (4.1%) in the aficamten group (5 participants from CY 6031 and 2 participants from CY 6021) and 1 participant (0.7%) in the placebo group (from CY 6031) had an LVEF < 50% (Table), with exposure-adjusted incidence rates of 8.6 and 1.3 persons per 100 person-years in the 2 treatment groups, respectively. 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%. 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).

Per site-read assessments of LVEF, 9 participants (5.3%) in the aficamten group (7 participants from CY 6031 and 2 participants from CY 6021) and 1 participant (0.7%) in the placebo group (from CY 6031) had an LVEF < 50% (Table), with exposure-adjusted incidence rates of 11.1 and 1.3 persons per 100 person-years in the 2 treatment groups, respectively. All 9 participants in the aficamten group had their dose down-titrated (as was specified in the study protocols when a site-read LVEF was < 50%), and subsequent LVEF values were all ≥ 50%. One participant (from CY 6021) had a site-read LVEF of 41.7% at Week 6 with a concurrent core laboratory LVEF of 58.2%; this participant had a temporally associated TEAE of peripheral oedema (worsening swelling of the hands and feet) of moderate severity but no other associated evidence that indicated clinical heart failure. The remaining 8 aficamten-treated participants had no associated signs or symptoms of heart failure. One placebo-treated participant with LVEF < 50% by both core lab and site read (48% and 45%, respectively) had an associated TEAE of peripheral oedema (Table).

In pivotal trial CY 6031, plasma concentrations of aficamten in participants with occurrences of LVEF < 50% were generally stable such that excursions of aficamten concentrations did not explain the incidents of decreased LVEF.

In Pool 2, small mean postbaseline decreases in LVEF were observed, similar to those in Pool 1. Nine participants (2.7%) had an LVEF < 50% per the core laboratory evaluation, 7 of these participants were included in Pool 1, thus reflecting 2 participants having a core laboratory LVEF < 50% in Study CY 6022. None of the 9 participants with core laboratory-assessed LVEF < 50% had associated signs or symptoms of potential heart failure. Four participants had either a subsequent down-titration of dose or washout period (ie, following the end of treatment in a parent study), after which the LVEF resolved to ≥ 50%. The EAIR for any postbaseline LVEF < 50% per core laboratory evaluation was 2.1 persons per 100 person-years (DCO 31AUG2024), which is substantially lower than the EAIR of 8.6 persons per 100 person-years observed in Pool 1, indicating stability of LVEF with long-term treatment.

Per local evaluation, a cumulative total of 15 participants (4.5%) had an LVEF < 50% (Table). Four of these participants (1.2%) had an AE associated with signs and symptoms of heart failure, which included ejection fraction decreased, peripheral edema, dyspnea, and cardiac failure. All 15 participants had a subsequent down-titration of dose, after which the LVEF resolved to ≥ 50% for most participants. For 1 participant, resolution occurred after dose down-titration and a temporary treatment interruption. For another participant, resolution occurred after down-titration with a first event of LVEF < 50%, but down-titration after a second event did not lead to resolution by the time the participant was withdrawn from the study. This participant had multiple occurrences of LVEF < 50% and peripheral edema while on placebo in the parent study (CY 6031). The EAIR for any postbaseline LVEF < 50% per local evaluation was 3.6 persons per 100 person-years, which is substantially lower than the EAIR of 11.1 persons per 100 person-years observed in Pool 1, indicating stability of LVEF with long-term treatment.

Table 65: Summary of Treatment-emergent LVEF Decreases (Pool 1 and Pool 2, Safety Analysis Set) (Source: Table 31, summary of clinical safety).

Clinical Outcome	Pool 1		Pool 2
	Aficamten (N = 170) n (%)	Placebo (N = 153) n (%)	Aficamten (N = 335) n (%)
Core Laboratory Evaluation			
LVEF < 40%	1 (0.6)	0	1 (0.3)
LVEF < 50%	7 (4.1)	1 (0.7)	9 (2.7)
EAIR for LVEF < 50% (persons per 100 person-years)	8.61	1.29	2.10
LVEF < 50% and Followed by Down-titration or Washout Period	4 (2.4)	0	4 (1.2)
LVEF < 50% to ≥ 50% After Down-titration or Washout Period[a]	4 (100)	0	4 (100)
LVEF < 50% and Followed by Down-titration	1 (0.6)	0	1 (0.3)
LVEF < 50% to ≥ 50% After Down-titration[a]	1 (100)	0	1 (100)
LVEF < 50% With Signs or Symptoms of Potential Heart Failure[b]	0	1 (0.7)	0
Site-read Evaluation			
LVEF < 40%	0	0	0
LVEF < 50%	9 (5.3)	1 (0.7)	15 (4.5)
EAIR for LVEF < 50% (persons per 100 person-years)	11.11	1.29	3.55
LVEF < 50% and Followed by Down-titration or Washout Period	9 (5.3)	0	15 (4.5)
LVEF < 50% to ≥ 50% After Down-titration or Washout Period[a]	9 (100)	0	15 (100)
LVEF < 50% and Followed by Down-titration	9 (5.3)	0	15 (4.5)
LVEF < 50% to ≥ 50% After Down-titration[a]	9 (100)	0	15 (100)
LVEF < 50% With Signs or Symptoms of Potential Heart Failure[b]	1 (0.6)	1 (0.7)	4 (1.2)

EAIR = exposure-adjusted incidence rate; 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 met 1 criterion 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.

Evaluation of Potential Rebound

Pivotal phase 3 trial (CY 6031)

An assessment for potential rebound during the per-protocol washout period (ie, between EOT [Week 24] and EOS [Week 28]) was performed prior to unblinding as defined by a supplemental SAP. The potential rebound effect was defined as the emergence of new disease related symptoms or worsening of prior symptoms relative to those present at baseline. This potential rebound effect was distinguished from recurrence of the underlying disease in the absence of pharmacological drug activity after treatment discontinuation.

Participants with CV AEs (customized standard query) with an onset during the washout period were identified (23 who had received aficamten during the study and 9 who had received placebo; see Listing 16.2.7.4 for participant identification numbers). A medical review of the participants was conducted after database lock in a blinded manner (ie, treatment assignment was unknown by the reviewers). The condition of potential rebound was met if the participant experiencing the CV AE also met all 3 of the following criteria: 1) a 30% increase from baseline in NT-proBNP; 2) a resting and/or Valsalva LVOT-G increase from baseline; and 3) a > 1 class increase from baseline in NYHA class and/or a > 15-point decrease from baseline in KCCQ-CSS. Of the participants identified with a CV AE during the washout period, 4 met the 3 criteria required for potential rebound. Two of the 4 participants were found, during the blinded medical review, to have alternative etiology responsible for the CV AE and other findings (1 participant with a decline in hemoglobin of > 2 g, and 1 with non-cardiac syncope). After unblinding, it was found that the participant with syncope was treated with placebo during the study.The remaining 2 participants, both in the aficamten group, satisfied the predefined criteria for potential rebound, and the blinded medical review did not identify any important confounders. These participants experienced the following postdose AEs: worsening HCM (of moderate severity) reported for 1 participant, and dyspnea and palpitations (both of mild severity) reported for the other participant.

2.6.8.4. Laboratory findings

Haematology

Integrated safety analysis – Pools 1, 2 and 3

In Pool 1, mean changes in haematology parameters from baseline during the treatment period and the posttreatment washout period were small and similar between the aficamten group and the placebo group. Similarly, the proportion of participants who had shifts in values from normal at baseline to below the lower limit of normal (LLN) or above the ULN at any time postbaseline were similar between the aficamten and placebo groups.

In Pool 2 and Pool 3, mean changes in haematology parameters from baseline during treatment were also relatively small and consistent with those observed for the aficamten group in Pool 1. The proportion of participants who had shifts in values from normal at baseline to below the LLN or above the ULN at any time postbaseline were generally consistent with those observed in the aficamten group in Pool 1.

Serum Chemistry

Integrated safety analysis – Pools 1, 2 and 3

Serum Chemistry Values Over Time

In Pool 1, mean changes in serum chemistry parameters from baseline during the treatment period and posttreatment washout period were relatively small and similar between the aficamten and placebo treatment groups. Shifts in serum chemistry values from normal at baseline to below the LLN or above the ULN at any time postbaseline appeared to occur at similar frequencies between the aficamten and placebo groups.

Pool 2 and Pool 3 showed similar results to those of the aficamten group in Pool 1.

Abnormalities in Liver Function Tests

In Pool 1, abnormalities in ALT, AST, or bilirubin (ie, > ULN) were observed with generally similar incidence between the aficamten and placebo groups. Similar incidences of these abnormalities were

also observed between treatment groups for only those participants with normal values at baseline. For most participants, abnormal values were just outside the reference range and were not clinically meaningful. Among participants with normal values at baseline who were in the aficamten group, 2 participants had ALT and/or AST > 3 × ULN postbaseline as follows:

- One participant with normal values at baseline and throughout the treatment period developed elevated AST of 7 × ULN at Week 24 (with ALT of 1.9 × ULN and total bilirubin and ALP within normal limits) and concurrent elevations of creatine kinase (> 16500 U/L, ULN 207 U/L) and lactate dehydrogenase (931 U/L, ULN 281 U/L), suggesting a non-hepatic origin.
- One participant had elevated ALT at 3.1 × ULN at Week 24 (with AST of 1.2 × ULN and total bilirubin and ALP within normal limits), which normalized by the next assessment time point (Week 28). At Week 16, the participants had a TEAE of hepatic cytolysis (with ALT of 2.7 × ULN, AST 1.5 × ULN, total bilirubin not provided) in the context of an ongoing TEAE of cardiac failure.

In Pool 2, 1 additional participant had a transient elevation of ALT > 3 × ULN at Week 24 (with AST of 2.3 × ULN), which resolved.

The incidence of postbaseline abnormalities in Pool 2 and Pool 3 were consistent with those observed for the aficamten group in Pool 1.

Hepatic TEAEs of interest are described above. No participant met Hy's law criteria. Overall, liver function tests showed no signal of hepatotoxicity with aficamten.

Urinalysis

Integrated safety analysis – Pools 1, 2 and 3

In Pool 1, the proportion of participants with shifts from a normal value at baseline to a low or high value postbaseline was similar between the aficamten and placebo groups for each urinalysis parameter.

The results in Pool 2 and Pool 3 were consistent with those for the aficamten group in Pool 1.

Cardiac Biomarkers

Integrated safety analysis – Pools 1 and 2

N-Terminal Pro-B-Type Natriuretic Peptide

In Pool 1, baseline NT-proBNP concentrations were ≥ ULN for 89.2% of participants in the aficamten group and 89.4% of participants in the placebo group, and concentrations were ≥ 5 × ULN for 55.1% of participants in the aficamten group and 52.3% of participants in the placebo group. After initiation of IP, postbaseline NT proBNP concentrations decreased substantially in the aficamten group and showed little change in the placebo group (Figure). At Week 8, 90.6% of the aficamten group, compared with 43.8% of the placebo group, had an NT-proBNP concentration < 5 × ULN. The decreased NT-proBNP concentrations were maintained until participants completed treatment; values returned to baseline in the posttreatment washout period.

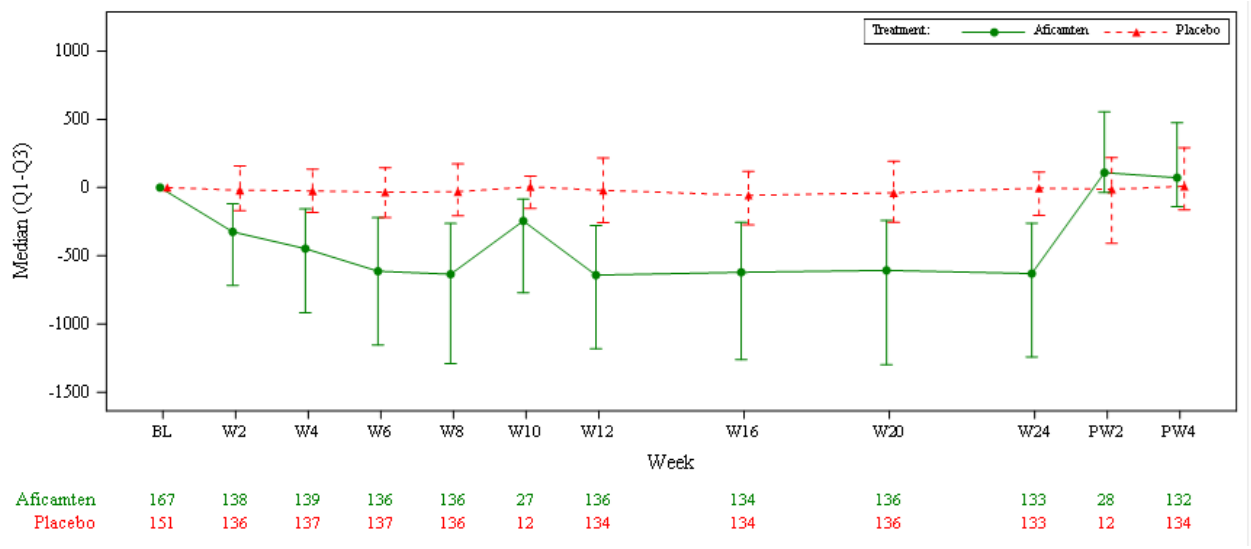


Figure 30: Pool 1: Change (ng/L) From Baseline in NT-proBNP (Safety Analysis Set) (Source: Figure 1, Summary of Clinical Safety).

BL = baseline; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PW2 = posttreatment Week 2 (CY 6021 Week 12); PW4 = posttreatment Week 4 (CY 6031 Week 28); Q1 = first quantile; Q3 = third quantile; W = Week. Baseline was defined as the last data collected before the first dose. Visits are as scheduled in CY 6021 and CY 6031. Visits were not pooled if on treatment in 1 study and posttreatment in another. Visits with n < 10 participants were not plotted. Note: The apparent increase in NT-proBNP at Week 10 for the aficamten group relates to the differences in baseline NT-proBNP values in the small sample of participants at Week 10 derived from CY 6021 only.

In Pool 2 and Pool 3, substantial decreases from baseline were observed and sustained with continued aficamten treatment.

High-Sensitivity Cardiac Troponin I

In Pool 1, baseline hs-cTnI concentrations were ≥ ULN for 27.6% of participants in the aficamten group and 26.1% of participants in the placebo group. hs cTnI concentrations decreased from baseline for participants in the aficamten group and showed little change from baseline in the placebo group (Figure). Decreased hs-cTnI concentrations in the aficamten group were maintained through the treatment period and returned to baseline during the posttreatment washout period.

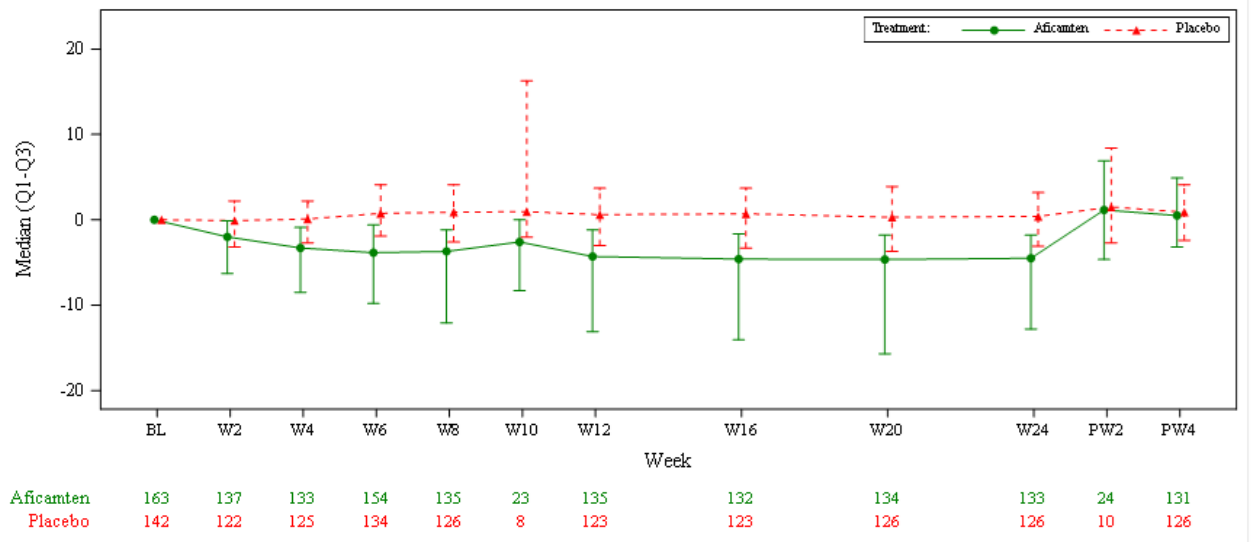


Figure 31: Pool 1: Change (ng/L) From Baseline in hs-cTnI (Safety Analysis Set) (Source: Figure 2, Summary of Clinical Safety).

BL = baseline; hs-cTnI = high-sensitivity cardiac troponin I; PW2 = posttreatment Week 2 (CY 6021 Week 12); PW4 = posttreatment Week 4 (CY 6031 Week 28); Q1 = first quantile; Q3 = third quantile; W = Week. Baseline was defined as the last data collected before the first dose. Visits are as scheduled in CY 6021 and CY 6031. Visits were not pooled if on treatment in 1 study and posttreatment in another. Visits with n < 10 participants were not plotted.

In Pool 2 and Pool 3, hs-cTnI concentrations decreased from baseline following the start of aficamten; the decreased values were maintained during ongoing treatment.

Vital Signs

Pivotal phase 3 trial (CY 6031)

Vital signs (systolic and diastolic BPs, heart rate, respiratory rate, BMI, height, and weight) at each assessment time point and associated changes from baseline are summarized in Table . During the study, small mean and median increases from baseline in systolic and diastolic BP were observed in the aficamten group but not the placebo group (Table). The mean increases were sustained throughout the treatment period and returned to baseline values during the washout period.

Table 66: Changes From Baseline in Systolic and Diastolic Blood Pressure (Source: Table 46, CY6031 Clinical Study Report).

	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)	
	Aficamten (N=142)	Placebo (N = 140)	Aficamten (N=142)	Placebo (N = 140)
Baseline				
n	142	140	142	140
Mean (SD)	124.6 (15.90)	125.7 (16.02)	74.6 (10.70)	74.1 (10.58)
Median	123.5	124.0	74.0	74.0
Q1, Q3	113.0, 135.0	115.5, 136.0	67.0, 81.0	68.0, 80.5
Change at Week 12				
N	140	137	140	137
Mean (SD)	3.5 (14.57)	-2.2 (14.51)	3.6 (8.74)	0.3 (8.49)
Median	3.0	-3.0	4.0	0.0
Q1, Q3	-6.0, 12.0	-11.0, 6.0	-2.0, 9.0	-4.0, 4.0
Change at Week 24				
n	139	137	139	137
Mean (SD)	2.3 (13.31)	-2.7 (14.47)	3.1 (7.74)	-0.9 (8.65)
Median	3.0	-3.0	4.0	0.0
Q1, Q3	-7.0, 11.0	-11.0, 5.0	-1.0, 8.0	-7.0, 4.0
Change at Week 28				
n	138	136	138	136
Mean (SD)	-2.4 (15.35)	-2.8 (15.16)	-1.6 (9.45)	-0.4 (8.77)
Median	-2.0	-3.0	-1.0	0.0
Q1, Q3	-13.0, 7.0	-10.0, 6.5	-6.0, 5.0	-5.0, 5.0

Participants with potentially clinically significant vital signs are summarized in Table . The incidence of potentially clinically significant elevations in BP was similar between treatment groups at baseline but

was higher in the aficamten group than in the placebo group postbaseline. Elevated systolic BP (≥ 160 mmHg) at baseline was observed in 1.4% and 2.9% of participants in the aficamten and placebo groups, respectively; postbaseline, the incidences increased to 15.5% and 7.9% in the 2 groups, respectively. Similarly, elevated diastolic BP (≥ 100 mmHg) at baseline was observed in 1.4% and 0.7% of participants in the 2 treatment groups, respectively; postbaseline, the incidences increased to 6.3% and 2.9%, respectively. Evaluation of hypertension AEs can be found in earlier section above.

Table 67: Summary of Potentially Clinically Significant Postbaseline Vital Sign Values (Safety Analysis Set) (Source: Table 47, CY6031 Clinical Study Report).

Parameter	Baseline		Postbaseline	
	Aficamten (N=142) n/N1 (%)	Placebo (N=140) n/N1 (%)	Aficamten (N=142) n/N1 (%)	Placebo (N=140) n/N1 (%)
Systolic BP				
≤ 80 mmHg	0/142	0/140	1/142 (0.7)	2/140 (1.4)
≥ 160 mmHg	2/142 (1.4)	4/140 (2.9)	22/142 (15.5)	11/140 (7.9)
Diastolic BP				
≤ 50 mmHg	2/142 (1.4)	2/140 (1.4)	7/142 (4.9)	8/140 (5.7)
≥ 100 mmHg	2/142 (1.4)	1/140 (0.7)	9/142 (6.3)	4/140 (2.9)
Heart rate				
≤ 50 bpm	6/142 (4.2)	9/140 (6.4)	16/142 (11.3)	32/140 (22.9)
≥ 120 bpm	0/142	0/140	0/142	0/140
Respiratory rate				
> 18 breaths/min	20/140 (14.3)	26/140 (18.6)	67/142 (47.2)	72/140 (51.4)

BP = blood pressure. Notes: Baseline assessments were defined as the last non-missing measurement prior to administration of the first dose of study treatment. Percentages were based on the number of dosed participants with at least 1 postbaseline value for each parameter (N1). If a participant had multiple results meeting the criteria, the participant was only counted once under each category.

Integrated safety analysis – Pools 1, 2 and 3

For Pool 1, which included only participants with oHCM, small mean and median increases from baseline in systolic and diastolic BP were observed in the aficamten group after the start of dosing, whereas the placebo group showed minimal changes from baseline (Table). The mean increases in the aficamten group were sustained throughout the treatment period and returned to baseline values during the washout period.

In Pool 2, which also included only participants with oHCM, data are consistent with those of Pool 1, with small mean and median increases from baseline in systolic and diastolic BP during dosing with aficamten.

In Pool 3, which included only participants with nHCM, minimal to no changes from baseline in systolic and diastolic BP were observed with aficamten treatment (Table).

Table 68: Changes From Baseline in Systolic and Diastolic Blood Pressure (Pool 1, Safety Analysis Set) (Source: Table 29, Summary of Clinical Safety).

	Systolic BP (mmHg)		Diastolic BP (mmHg)	
	Aficamten (N = 170)	**Placebo (N = 153)**	**Aficamten (N = 170)**	**Placebo (N = 153)**
Baseline				
N	170	153	170	153
Mean (SD)	124.3 (15.94)	125.6 (15.68)	74.2 (10.47)	73.9 (10.38)
Median (Min, Max)	123.5 (84, 166)	125.0 (84, 172)	74.0 (48, 102)	74.0 (42, 119)
Change at Week 6				
N	169	150	169	150
Mean (SD)	4.8 (14.62)	-1.7 (13.38)	2.6 (8.40)	-0.3 (7.89)
Median (Min, Max)	3.0 (-31, 60)	-2.5 (-44, 38)	3.0 (-33, 24)	-1.0 (-21, 32)
Change at Week 12				
N	140	137	140	137
Mean (SD)	3.5 (14.57)	-2.2 (14.51)	3.6 (8.74)	0.3 (8.49)
Median (Min, Max)	3.0 (-36, 50)	-3.0 (-42, 48)	4.0 (-19, 22)	0.0 (-27, 33)
Change at Week 24				
N	139	137	139	137
Mean (SD)	2.3 (13.31)	-2.7 (14.47)	3.1 (7.74)	-0.9 (8.65)
Median (Min, Max)	3.0 (-36, 52)	-3.0 (-37, 36)	4.0 (-21, 27)	0.0 (-24, 26)
Change at Posttreatment Week 4				
N	138	136	138	136
Mean (SD)	-2.4 (15.35)	-2.8 (15.16)	-1.6 (9.45)	-0.4 (8.77)
Median (Min, Max)	-2.0 (-46, 51)	-3.0 (-51, 37)	-1.0 (-31, 20)	0.0 (-29, 34)

BP = blood pressure; Max = maximum; Min = minimum; n = number of participants in the subgroup; N = number of participants; SD = standard deviation. Baseline was defined as the last data collected before the first dose. Visits were as scheduled in CY 6021 and CY 6031. Posttreatment Week 4 was CY 6031 Week 28. Visits were not pooled if on treatment in 1 study and posttreatment in another.

Table 69: Changes From Baseline in Systolic and Diastolic Blood Pressure (Pool 3, Safety Analysis Set) (Source: Table 30, Summary of Clinical Safety).

	Systolic BP (mmHg)	Diastolic BP (mmHg)
	Aficamten (N = 41)	Aficamten (N = 41)
Baseline		
N	41	41
Mean (SD)	122.0 (15.81)	70.8 (10.00)
Median (Min, Max)	119.0 (93, 166)	71.0 (51, 88)
Change at Week 6		
N	40	40
Mean (SD)	0.1 (12.72)	1.0 (8.47)
Median (Min, Max)	−1.5 (−19, 41)	−0.5 (−13, 28)
Change at Week 10		
N	40	40
Mean (SD)	−0.5 (12.50)	−0.3 (7.52)
Median (Min, Max)	0.5 (−32, 32)	0.0 (−18, 20)
Change at Week 12		
N	34	34
Mean (SD)	0.3 (12.84)	0.0 (10.58)
Median (Min, Max)	2.0 (−28, 21)	−1.0 (−25, 26)
Change at Week 22		
N	34	34
Mean (SD)	0.8 (16.03)	1.2 (11.89)
Median (Min, Max)	−0.5 (−36, 54)	−0.5 (−18, 40)

BP = blood pressure; Max = maximum; Min = minimum; n = number of participants in the subgroup; N = number of participants; SD = standard deviation. Baseline was defined as the last data collected before the first dose. Visits were as scheduled in CY 6021 and CY 6031. Posttreatment Week 4 was CY 6031 Week 28. Visits were not pooled if on treatment in 1 study and posttreatment in another.

Electrocardiograms

Pivotal phase 3 trial (CY 6031)

Electrocardiogram parameters (ECG mean heart rate, RR and PR intervals, QRS duration, QT,QTcB, and QTcF intervals) obtained at baseline and Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28 are summarized below. Postbaseline changes in these parameters were generally small and consistent between the aficamten and placebo treatment groups. Mean changes in these ECG parameters showed no trend and were not clinically meaningful.

The participant-incidences of maximum postbaseline QTcF values were consistent between treatment groups (Table). The participant incidence of shifts from baseline to a longer QTcF interval postbaseline was similar between treatment groups (31.0% aficamten, 31.4%) (Table 14.3.8.3). The maximum postbaseline change in QTcF was ≤ 30 msec for most participants in both treatment groups. A total of 4

participants (3 [2.1%] in the aficamten group and 1 [0.7%] in the placebo group) had an increase > 60 msec.

Table 70: Participants with Potentially Clinically Significant Postbaseline ECG Values (Safety Analysis Set) (Source: Table 48, CY 6031, Clinical Study Report).

QTcF Interval	Category	Aficamten (N=142)	Placebo (N=140)
Baseline Value	n	142	139
	≤ 450 msec	81 (57.0)	79 (56.8)
	> 450 to ≤ 480 msec	51 (35.9)	41 (29.5)
	> 480 to ≤ 500 msec	8 (5.6)	13 (9.4)
	> 500 msec	2 (1.4)	6 (4.3)
Maximum Postbaseline Value	n	142	140
	≤ 450 msec	53 (37.3)	56 (40.0)
	> 450 to ≤ 480 msec	68 (47.9)	52 (37.1)
	> 480 to ≤ 500 msec	12 (8.5)	18 (12.9)
	> 500 msec	9 (6.3)	14 (10.0)
Maximum Overall Change from Baseline	n	142	139
	≤ 30 msec	127 (89.4)	120 (86.3)
	> 30 to ≤ 60 msec	12 (8.5)	18 (12.9)
	> 60 msec	3 (2.1)	1 (0.7)

ECG = electrocardiogram; QTcF = Fridericia corrected QT. Notes: Baseline assessments were defined as the last non-missing measurement prior to administration of the first dose of study treatment.

Integrated safety analysis – Pools 1 and 2

Observed ECG Parameters

For Pool 1, ECG parameters (ECG mean heart rate, PR interval, QRS duration, QT interval, QT interval corrected by the Bazett formula (QTcB) and QTcF intervals, and RR interval) postbaseline changes were generally small and consistent between the aficamten and placebo treatment groups. Mean changes in these ECG parameters showed no trend and were not clinically meaningful.

The participant-incidences of maximum postbaseline QTcF, PR, and QRS values and categorical changes from baseline were consistent between treatment groups. For QTcF, the maximum postbaseline change was ≤ 30 msec for most participants in both treatment groups (88.8% aficamten, 85.5% placebo), and a maximum postbaseline shift of > 60 msec was observed for 3 participants (1.8%) in the aficamten group and 1 participant (0.7%) in the placebo group. Changes from baseline in QTcF did not appear to correlate with trough plasma concentrations of aficamten.

For Pool 2 (335 aficamten-treated participants), postbaseline changes in ECG parameters were generally small and appeared consistent with those described for Pool 1.

CY 6019: Evaluation of Aficamten on QT/QTc Interval

The effect of aficamten (50 mg) on QT/QTc interval was evaluated in healthy participants in CY 6019. The results from CY 6019 demonstrated lack of QTc prolongation by aficamten and its metabolites (CK 3834282 and CK 3834283) across the observed plasma concentration ranges of aficamten, CK-3834282, and CK-3834283 up to 1660, 213, and 343 ng/mL, respectively. The upper limits of the 90%

CI for predicted placebo-corrected change from baseline in QTcF for aficamten, CK 3834282, and CK 3834283 were all < 10 msec, confirming the lack of QTc prolongation by aficamten and its metabolites.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

The incidences of TEAEs were evaluated based on intrinsic factors of age, sex, race, and ethnicity. In addition, safety topics of interest were evaluated based on subgroups of baseline NYHA class, NT-proBNP concentration, and eGFR. Safety topics of interest were also evaluated based on extrinsic factors of beta-blocker use at baseline and beta-blocker use at baseline with a concomitant CCB or disopyramide.

These have been evaluated in pool 1.

Intrinsic Factors

Integrated safety analysis – Pool 1

Age

Subgroup analysis was performed for age subgroups < 65 years, ≥ 65 to < 75 years, and ≥ 75 years. There were no clinically meaningful differences in the incidences of overall or individual TEAEs by treatment group between the subgroups of < 65 years and ≥ 65 to < 75 years. However, the small number of individual TEAEs limits comparisons by subgroup. For participants ≥ 75 years, there were too few participants for meaningful comparisons.

For all age subgroups, there were too few data for TESAEs, cardiac failure TESAEs of interest, and cardiac failure TEAEs of interest for meaningful comparisons.

Table 71: Summary of the Overall Incidence of TEAEs by Age (Pool 1, Safety Analysis Set) (Source: Table 32, Summary of Clinical Safety).

Preferred Term[a]	< 65 Years		≥ 65 to < 75 Years		≥ 75 Years	
	Aficamten (N = 102) n (%)	Placebo (N = 94) n (%)	Aficamten (N = 54) n (%)	Placebo (N = 40) n (%)	Aficamten (N = 14) n (%)	Placebo (N = 19) n (%)
Participants With at Least 1 TEAE	73 (71.6)	67 (71.3)	40 (74.1)	33 (82.5)	13 (92.9)	10 (52.6)
Atrial Fibrillation	2 (2.0)	5 (5.3)	2 (3.7)	0	0	0
COVID-19	7 (6.9)	4 (4.3)	2 (3.7)	3 (7.5)	0	2 (10.5)
Dizziness	5 (4.9)	1 (1.1)	4 (7.4)	2 (5.0)	2 (14.3)	0
Dyspnea	8 (7.8)	5 (5.3)	2 (3.7)	3 (7.5)	1 (7.1)	0
Fatigue	0	5 (5.3)	3 (5.6)	2 (5.0)	1 (7.1)	1 (5.3)
Headache	7 (6.9)	11 (11.7)	6 (11.1)	3 (7.5)	1 (7.1)	0
Hypertension	7 (6.9)	4 (4.3)	2 (3.7)	0	2 (14.3)	0
Nausea	1 (1.0)	5 (5.3)	5 (9.3)	0	0	1 (5.3)
Palpitations	5 (4.9)	4 (4.3)	3 (5.6)	1 (2.5)	2 (14.3)	0
Upper Respiratory Tract Infection	8 (7.8)	8 (8.5)	1 (1.9)	4 (10.0)	0	0
Participants With at Least 1 TESAE	6 (5.9)	6 (6.4)	3 (5.6)	5 (12.5)	1 (7.1)	3 (15.8)
Participants With at Least 1 Cardiac TEAE of Interest[b]	23 (22.5)	16 (17.0)	11 (20.4)	6 (15.0)	3 (21.4)	5 (26.3)
Atrial Fibrillation	2 (2.0)	5 (5.3)	2 (3.7)	0	0	0
Dyspnea	8 (7.8)	5 (5.3)	2 (3.7)	3 (7.5)	1 (7.1)	0
Participants With at Least 1 Cardiac TESAEs of Interest	4 (3.9)	4 (4.3)	0	1 (2.5)	1 (7.1)	2 (10.5)
Participants With at Least 1 Cardiac TEAEs of Interest Leading to Discontinuation of IP	0	1 (1.1)	0	0	0	0

COVID-19 = coronavirus disease 2019; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; N = number of participants; SMQB = standardized MedDRA query broad; SMQN = standardized MedDRA query narrow; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event. a ≥ 5 participants in any treatment group. b Consisting of cardiac failure (SMQB + other PTs), ventricular tachyarrhythmias (SMQN + other PTs), supraventricular tachyarrhythmias (SMQB + other PTs).

Sex

For Pool 1, the number of participants in each group (female, male) and the incidence of TEAEs, TESAEs, cardiac failure TEAEs of interest, serious cardiac failure TEAEs of interest, and cardiac failure TEAEs of interest that led to discontinuation of IP are summarized by sex in Table .

For both female and male subgroups, there were too few data for TESAEs, cardiac TESAEs of interest, and cardiac failure TEAEs of interest leading to discontinuation of IP for meaningful comparisons. While

there were fewer TESAEs in the aficamten group compared with the placebo group overall, the incidence trended lower in the female subgroup and higher in the male subgroup in aficamten-treated participants (2.8% vs 8.1%, respectively).

Table 72: Summary of the Overall Incidence of TEAEs by Sex (Pool 1, Safety Analysis Set) (Source: Table 33, Summary of Clinical Safety).

Preferred Term[a]	Female		Male	
	Aficamten (N = 71) n (%)	Placebo (N = 67) n (%)	Aficamten (N = 99) n (%)	Placebo (N = 86) n (%)
Participants With at Least 1 TEAE	58 (81.7)	51 (76.1)	68 (68.7)	59 (68.6)
Asthenia	4 (5.6)	0	0	0
Fatigue	3 (4.2)	6 (9.0)	1 (1.0)	2 (2.3)
Cough	4 (5.6)	1 (1.5)	1 (1.0)	1 (1.2)
COVID-19	2 (2.8)	5 (7.5)	7 (7.1)	4 (4.7)
Dizziness	6 (8.5)	2 (3.0)	5 (5.1)	1 (1.2)
Dyspnea	5 (7.0)	5 (7.5)	6 (6.1)	3 (3.5)
HCM	4 (5.6)	4 (6.0)	2 (2.0)	0
Headache	7 (9.9)	8 (11.9)	7 (7.1)	6 (7.0)
Hypertension	5 (7.0)	3 (4.5)	6 (6.1)	1 (1.2)
Nasopharyngitis	1 (1.4)	2 (3.0)	5 (5.1)	4 (4.7)
Palpitations	7 (9.9)	3 (4.5)	3 (3.0)	2 (2.3)
Upper Respiratory Tract Infection	3 (4.2)	5 (7.5)	6 (6.1)	7 (8.1)
Participants With at Least 1 TESAE	2 (2.8)	11 (16.4)	8 (8.1)	3 (3.5)
Participants With at Least 1 Cardiac TEAE of Interest[b]	18 (25.4)	16 (23.9)	19 (19.2)	11 (12.8)
Dyspnea	5 (7.0)	5 (7.5)	6 (6.1)	3 (3.5)
HCM	4 (5.6)	4 (6.0)	2 (2.0)	0
Participants With at Least 1 Cardiac TESAE of Interest	1 (1.4)	5 (7.5)	4 (4.0)	2 (2.3)
Participants With at Least 1 Cardiac TEAE of Interest Leading to Discontinuation of IP	0	1 (1.5)	0	0

COVID-19 = coronavirus disease 2019; HCM = hypertrophic cardiomyopathy; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; N = number of participants; SMQB = standardized MedDRA query broad; SMQN = standardized MedDRA query narrow; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event. a ≥ 5% of participants in either treatment group. b Consisting of cardiac failure (SMQB + other PTs), ventricular tachyarrhythmias (SMQN + other PTs), supraventricular tachyarrhythmias (SMQB + other PTs).

Race

Analysis of the safety data was performed for race subgroups of White, Asian, Black or African American (with 3 participants in the aficamten group and 1 participant in the placebo group), and Other (with 2 participants in the aficamten group and 0 participants in the placebo group). For Pool 1, because there were so few participants who were Black or African American or Other, only the number of participants in the White and Asian subgroups and the corresponding incidence of TEAEs and TESAEs are summarized in Table .

Table 73: Summary of the Overall Incidence of TEAEs by Race (Pool 1, Safety Analysis Set) (Source: Table 34, Summary of Clinical Safety).

Preferred Term[a]	White		Asian	
	Aficamten (N = 136) n (%)	Placebo (N = 127) n (%)	Aficamten (N = 29) n (%)	Placebo (N = 25) n (%)
Participants With at Least 1 TEAE	98 (72.1)	93 (73.2)	25 (86.2)	17 (68.0)
Angina Pectoris	3 (2.2)	7 (5.5)	1 (3.4)	0
COVID-19	4 (2.9)	6 (4.7)	5 (17.2)	3 (12.0)
Dizziness	8 (5.9)	3 (2.4)	3 (10.3)	0
Dyspnea	7 (5.1)	6 (4.7)	4 (13.8)	2 (8.0)
Fatigue	4 (2.9)	6 (4.7)	0	2 (8.0)
Headache	13 (9.6)	12 (9.4)	1 (3.4)	2 (8.0)
Hypertension	8 (5.9)	4 (3.1)	2 (6.9)	0
Nasopharyngitis	5 (3.7)	6 (4.7)	1 (3.4)	0
Nausea	5 (3.7)	6 (4.7)	0	0
Pain in Extremity	5 (3.7)	2 (1.6)	0	0
Palpitations	7 (5.1)	5 (3.9)	3 (10.3)	0
Upper Respiratory Tract Infection	4 (2.9)	7 (5.5)	5 (17.2)	5 (20.0)
Participants With at Least 1 TESAE	10 (7.4)	12 (9.4)	0	2 (8.0)

COVID-19 = coronavirus disease 2019; n = number of participants with an event; N = number of participants; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event. a ≥ 5 participants in any treatment group.

Ethnicity

Analysis of the safety data was performed for ethnicity subgroups of Hispanic or Latino (consisting in Pool 1 of 3 participants in the aficamten group and 6 participants in the placebo group), not Hispanic or Latino (consisting of 156 participants in the aficamten group and 143 participants in the placebo group), and not reported (consisting of 11 participants in the aficamten group and 4 participants in the placebo group). The relatively few participants in 2 of the 3 subgroups preclude meaningful comparison of the safety data.

Evaluation of Safety Topics of Interest by Subgroups

Integrated safety analysis – Pool 1

NYHA class

Cardiac TEAEs of interest were analysed by baseline NYHA class: II, III, and IV. Because of there was only 1 participant who was NYHA class IV, only subgroups of NYHA class II and III are summarized for Pool 1 in Table .

For participants with a baseline NYHA class II in Pool 1, dyspnoea was the most frequently reported cardiac TEAE of interest (9 participants [7.2%] aficamten, 5 participants [4.3%] placebo). For participants with a baseline NYHA class III, dyspnoea was also frequently reported (2 participants [4.4%] aficamten, 2 participants [5.7%] placebo) along with HCM (3 participants [6.7%] aficamten, 0 participants placebo). As noted previously, the majority of cardiac failure TEAEs, including dyspnoea,

and all TEAEs of HCM in aficamten-treated participants were reported during the washout period. There were too few cardiac TESAEs of interest for meaningful comparison.

No participant in any NYHA class subgroup died due to a cardiac failure TEAE of interest. No participant treated with aficamten in any NYHA class subgroup discontinued treatment due to a cardiac failure TEAE of interest; and 1 participant in the placebo group with NYHA class II discontinued treatment due to a TEAE of loss of consciousness.

Table 74: Summary of the Overall Incidence of Cardiac TEAEs and TESAEs of Interest of by Baseline NYHA Class (Pool 1, Safety Analysis Set) Source: Table 35, Summary of Clinical Safety).

Cardiac Event of Interest Preferred Term[a]	NYHA Class II		NYHA Class III	
	Aficamten (N = 125) n (%)	Placebo (N = 117) n (%)	Aficamten (N = 45) n (%)	Placebo (N = 35) n (%)
Participants With at Least 1 TEAE	28 (22.4)	20 (17.1)	9 (20.0)	6 (17.1)
Dyspnea	9 (7.2)	5 (4.3)	2 (4.4)	2 (5.7)
HCM	3 (2.4)	4 (3.4)	3 (6.7)	0
Oedema Peripheral	1 (0.8)	0	1 (2.2)	2 (5.7)
Participants With at Least 1 TESAE	2 (1.6)	5 (4.3)	3 (6.7)	2 (5.7)

HCM = hypertrophic cardiomyopathy; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; N = number of participants; NYHA = New York Heart Association; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event. a ≥ 5% participants in any treatment group.

N-Terminal Pro-B-Type Natriuretic Peptide

Cardiac TEAEs of interest were analysed by NT-proBNP concentrations ≤ the median value versus > the median value at baseline (86.6 pmol/L). The overall incidences of cardiac TEAEs and TESAEs of interest are summarized for Pool 1 in Table .

For participants in Pool 1 with a baseline NT-proBNP concentration ≤ the median value, dyspnoea was the most frequently reported cardiac TEAE of interest (7 participants [8.6%] aficamten, 4 participants [5.1%] placebo). For participants in Pool 1 with a baseline NT-proBNP concentration > the median value, dyspnoea was also frequently reported (4 participants [4.7%] aficamten, 4 participants [5.5%] placebo) along with HCM (4 participants [4.7%] aficamten, 2 participants [2.7%] placebo). As noted previously, the majority of cardiac TEAEs in aficamten-treated participants, including dyspnoea and HCM, were reported during the washout period. There were too few cardiac TESAEs of interest for meaningful comparison.

No participant in either treatment group of either subgroup died due to a cardiac TEAE of interest. No participant treated with aficamten in either subgroup discontinued treatment due to a cardiac TEAE of interest; and 1 participant in the placebo group with an NT-proBNP concentration ≤ the median value discontinued treatment due to a TEAE of loss of consciousness.

Table 75: Summary of the Overall Incidence of Cardiac TEAEs and TESAEs by Baseline NT-proBNP Concentration (Pool 1, Safety Analysis Set) (Source: Table 36: Summary of Clinical Safety).

Cardiac TEAE of Interest Preferred Term[a]	Baseline NT-proBNP ≤ Median		Baseline NT-proBNP > Median	
	Aficamten (N = 81) n (%)	Placebo (N = 78) n (%)	Aficamten (N = 86) n (%)	Placebo (N = 73) n (%)
Participants With at Least 1 TEAE	15 (18.5)	12 (15.4)	21 (24.4)	15 (20.5)
Dyspnea	7 (8.6)	4 (5.1)	4 (4.7)	4 (5.5)
Participants With at Least 1 TESAE	2 (2.5)	2 (2.6)	3 (3.5)	5 (6.8)

MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with an event; N = number of participants; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event. a ≥ 5% participants in any treatment group.

eGFR

Renal function TEAEs of interest (per the SMQs of acute renal failure and chronic kidney disease) were analyzed by eGFR subgroups of 30 to < 60, 60 to < 90, and ≥ 90 mL/min/1.73 m2. The overall incidences of renal function TEAEs and TESAEs of interest are summarized by these subgroups for Pool 1 in Table .

Table 76: Summary of the Overall Incidence of Renal Function TEAEs and TESAEs by eGFR (Pool 1, Safety Analysis Set) (Source: Table 37, Summary of Clinical Safety).

eGFR:	30 - < 60 mL/min/1.73 m²		60 - < 90 mL/min/1.73 m²		≥ 90 mL/min/1.73 m²	
Participants With at Least 1:	Aficamten (N = 16) n (%)	Placebo (N = 8) n (%)	Aficamten (N = 83) n (%)	Placebo (N = 76) n (%)	Aficamten (N = 71) n (%)	Placebo (N = 69) n (%)
Renal Function TEAE of Interest	1 (6.3)	0	1 (1.2)	2 (2.6)	0	3 (4.3)
Renal Function TESAE of Interest	0	0	0	0	0	0

eGFR = estimated glomerular filtration rate; n = number of participants with an event; N = number of participants; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

Extrinsic Factors

Integrated safety analysis – Pool 1

Evaluation of Cardiac TEAEs by Beta-blocker Use at Baseline

Cardiac TEAEs of interest were analysed by baseline beta-blocker use (Table). As noted previously, the majority of cardiac failure TEAEs in aficamten-treated participants, including dyspnoea, were reported during the washout period.

For participants in Pool 1 using a beta-blocker at baseline, the most frequently reported cardiac TEAEs of interest (reported for > 4% of participants in either treatment group) were dyspnoea (4 participants [3.8%] aficamten, 4 participants [4.1%] placebo) and atrial fibrillation (2 participants [1.9%] aficamten, 4 participants [4.1%] placebo).

For participants in Pool 1 not using a baseline beta-blocker, the most frequently reported cardiac TEAEs of interest (reported for > 4% of participants in either treatment group) were dyspnoea (5 participants

[8.9%] aficamten, 4 participants [7.5%] placebo) and HCM (4 participants [7.1%] aficamten, 1 participant [1.9%] placebo).

There were too few cardiac TESAEs of interest for meaningful comparison.

No participant in either subgroup died due to a cardiac TEAE event of interest. No participant treated with aficamten in either subgroup discontinued treatment due to a cardiac TEAE of interest, but treatment was discontinued for 1 participant in the placebo group who was not using a beta-blocker at baseline.

Table 77: Summary of the Overall Incidence of Cardiac Failure TEAEs and TESAEs of Interest by Use of Beta-blockers at Baseline (Pool 1, Safety Analysis Set) (Source: Table 38, Summary of Clinical Safety).

	Beta-blocker Use at Baseline		No Beta-blocker Use at Baseline	
Participants With at Least 1:	**Aficamten (N = 106) n (%)**	**Placebo (N = 98) n (%)**	**Aficamten (N = 56) n (%)**	**Placebo (N = 53) n (%)**
Cardiac TEAEs of Interest	18 (17.0)	16 (16.3)	15 (26.8)	11 (20.8)
Cardiac TESAEs of Interest	3 (2.8)	5 (5.1)	2 (3.6)	2 (3.8)

n = number of participants with an event; N = number of participants; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Evaluation of Cardiac TEAEs by Concomitant Use of a Calcium Channel Blocker or Disopyramide With a Beta-blocker at Baseline

Cardiac TEAEs of interest were analysed by concomitant use of a beta-blocker with a CCB or with disopyramide versus a beta-blocker alone at baseline. The overall incidence of cardiac TEAEs and TESAEs of interest are summarized by these subgroups in Table . As noted previously, the majority of cardiac failure TEAEs in aficamten-treated participants were reported during the washout period.

Table 78: Pool 1: Summary of the Overall Incidence of Cardiac TEAEs and TESAEs of Interest by Use of Concomitant Calcium Channel Blocker or Disopyramide With a Beta-blocker (Safety Analysis Set) (Source: Table 39, Summary of Clinical Safety).

	Beta-blocker + CCB or Disopyramide		Beta-blocker Alone	
Participants With at Least 1 of the Following:	**Aficamten (N = 29) n (%)**	**Placebo (N = 32) n (%)**	**Aficamten (N = 77) n (%)**	**Placebo (N = 66) n (%)**
Cardiac TEAE of Interest	7 (24.1)	4 (12.5)	11 (14.3)	12 (18.2)
Cardiac TESAE of Interest	1 (3.4)	1 (3.1)	2 (2.6)	4 (6.1)

CCB = calcium channel blocker; n = number of participants with an event; N = number of participants; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Use in Pregnancy and Lactation

While nonclinical reproductive toxicity studies do not indicate any evidence of embryo-lethality or teratogenicity, it is not known whether aficamten can cause foetal harm when administered to a pregnant woman. Aficamten should only be used in a pregnant woman if the potential benefit justifies the potential risk to the foetus.

Two pregnancies were reported during clinical development of aficamten. The first pregnancy occurred in a female participant in CY 6022 who had received 10 mg QD aficamten prior to the pregnancy. The

pregnancy was planned with the participant's medical team (PTs of in vitro fertilization and maternal exposure before pregnancy); the participant underwent in vitro fertilization approximately 21 days after the last dose of aficamten. The participant had a full term delivery, and the baby was reported as born with normal physical status. The participant was breastfeeding at the time of the report.

The second pregnancy occurred in a female partner of a participant in CY 6022 who received 20 mg QD aficamten (PT of paternal exposure during pregnancy). The pregnancy was confirmed as planned, and there was no interruption of aficamten at the time of conception. No complications were reported during the pregnancy, and the baby was born full term at Week 39 of gestation. The baby was reported as healthy.

There are no data regarding the presence of aficamten or its metabolites in human milk, or its effects on the breastfed infant or on milk production. Due to the inability to monitor exposure to aficamten in infants, women are not advised to breastfeed during treatment with aficamten.

Overdose

There have been no reports of overdose with aficamten.

In the event of overdose, close monitoring of LVEF and vital signs is recommended. While there is no established treatment for an overdose, the use of rescue medications to treat low cardiac output (e.g., dobutamine) is recommended if necessary.

Drug Abuse

No studies of drug abuse or dependence were conducted. Aficamten is not chemically or pharmacologically similar to drugs with known abuse potential, and it does not produce psychoactive effects. There is no evidence to suggest that aficamten has the potential for abuse or misuse.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No evaluation of the effects on the ability to drive or operate machinery or impaired mental ability was performed for studies of aficamten. There is no pharmacological basis or clinical evidence that aficamten would affect the ability to operate machinery or cause impaired mental ability.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

See pharmacology section.

2.6.8.9. Discontinuation due to adverse events

Treatment-emergent Adverse Events Leading to Early Discontinuation of the Investigational Product

Pivotal phase 3 trial (CY 6031)

Study treatment was discontinued early due to a TEAE for 1 participant (0.7%) in the aficamten group and 2 participants (1.4%) in the placebo group. In the aficamten group, the TEAE that led to treatment discontinuation was mild paranoia, considered not related to the IP. In the placebo group, the TEAEs that led to treatment discontinuation were severe loss of consciousness and severe acute lymphocytic leukemia; both TEAEs met serious criteria and both were considered not related to IP.

Integrated safety analysis – Pools 1 and 2

In Pool 1, 1 participant (0.6%) in the aficamten group and 2 participants (1.3%) in the placebo group discontinued treatment due to a TEAE. TEAEs that led to discontinuation of treatment were paranoia (1 participant in the aficamten group) and acute lymphocytic leukemia and loss of consciousness (1 participant each in the placebo group). In Pool 2, only 1 participant (0.4%; the same participant noted in the aficamten group of Pool 1) discontinued treatment due to a TEAE (paranoia).

Treatment-emergent Adverse Events Leading to Dose Interruption

Integrated safety analysis – Pools 1 and 2

In Pool 1, TEAEs led to dose interruption for 2 participants (1.2%) in the aficamten group and 2 participants (1.3%) in the placebo group. TEAEs that led to dose interruption in the aficamten group were COVID-19 and cholecystitis, and those in the placebo group were pneumonia and squamous cell carcinoma of the oral cavity. In Pool 2, 5 participants (1.8%) had a TEAE that led to dose interruption; these TEAEs were COVID-19 (2 participants) and atrial fibrillation, cholecystitis, and hypertensive urgency (1 participant each).

2.6.8.10. Post marketing experience

Not applicable, as aficamten has not been marketed in any country, region, or territory for any indication.

2.6.9. Discussion on clinical safety

The **main source for the clinical safety evaluation** of aficamten is the pivotal phase 3 study (CY 6031), supported by an integrated (pooled) safety data analysis. Pool 1 consisted of placebo-controlled data from the 24-weeks pivotal phase 3 study (CY6031) and the 10-weeks phase 2 dose-finding study (CY 6021). Pool 2 contained longer term data from the ongoing open-label extension trial (OLE trial; CY 6022), plus the placebo-controlled data of the pivotal phase 3 study and the phase 2 dose-finding study. Pools 3 (consisting of data from nHCM participants) and 4 (containing data of healthy participants or participants with moderate hepatic impairment) are considered less relevant, since they do not consist of the target population and contain only short-term data.
Therefore, the focus of the clinical safety assessment will mostly be on the pivotal phase 3 study and pools 1 (placebo-controlled data) and 2 (longer-term data).

In the pivotal phase 3 trial, 282 participants (n=142 aficamten and n=140 placebo) were **exposed** to study medication and were included in the safety analysis. Of the 142 participants treated with aficamten, the majority of the patients needed the highest doses of 15 mg or 20 mg QD for an adequate response, as the week-24 dose was 5 mg QD for 5 participants (3.6%), 10 mg QD for 21 participants (15.3%), 15 mg QD for 48 participants (35.0%) and 20 mg QD for 63 patients (46.0%).
In the integrated safety analysis, a total of 323 (n=170 on aficamten and n=153 on placebo) participants were included in pool 1 and 335 participants in pool 2. In pool 1, the mean aficamten exposure duration was 5.0 months (0.9-6.8 months). Of the 335 participants in pool 2, the mean duration of aficamten exposure was increased to 15.2 months (0.1-41.5 months), with a duration of >6 months for 267 participants (79.7%), >12 months for only 198 participants (59.1%), and >24 months for 47 participants (14.0%).
According to the requirements of the *ICH E1 Guideline on the extent of population exposure to assess*

clinical safety for drugs intended for long-term treatment of non-life-threatening conditions, 100 patients exposed for a minimum of 1 year is considered to be acceptable for a safety database at dosage levels intended for clinical use. The documented safety exposure of pool 2 consists of 198 patients exposed to aficamten for >12 months and can, therefore, be considered sufficient. Furthermore, the applicant is proposing a meta-analysis (of CY 6031 and CY 6032) to allow an adequate evaluation of the CV safety profile of aficamten, according to the *EMA Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)*. This proposal with continuous monitoring of the cardiovascular safety of aficamten by routine pharmacovigilance, and by a planned real world observational study was agreed and considered acceptable.

In the pivotal phase 3 study, **adverse events** (AEs) were frequently reported, and the incidence of AEs was generally balanced between treatment groups (n=105, 73.9% aficamten vs n=99, 70.7% placebo), of which most were mild or moderate in severity. The most frequently reported (≥ 5%) AEs in the pivotal phase 3 trial were headache (7.7% aficamten, 7.1% placebo), hypertension (7.7% aficamten, 2.1% placebo) and palpitations (7.0% aficamten, 2.9% placebo). In pools 1 and 2, results were generally comparable.
Importantly, notable imbalances in the AEs of cardiac failure, hypertension, dizziness and palpitations were observed, both in the pivotal phase 3 study and in pool 1, and are further discussed below. Further, based on the information and discussion on AEs with lower incidences (i.e. ≥1%) no new safety signals have been revealed.

No **deaths** have been reported in the pivotal phase 3 trial and in pools 1 and 2 of the integrated safety analyses.
In the pivotal phase 3 study, the incidence of **serious adverse events** (SAEs) was relatively low with even a lower incidence in the aficamten group compared with the placebo group (n=8, 5.6% aficamten vs n=13, 9.3% placebo), which is reassuring. The most frequent reported SAEs were HCM worsening of symptoms (n=3, 2.1% aficamten vs n=1, 0.7% placebo) and atrial fibrillation (n=1, 0.7% vs n=1, 0.7%, respectively). Generally similar findings were seen in pools 1 and 2. No other specific patterns for a unexpected safety signal could be identified from the current available SAE safety data.

Several **adverse events of special interest** (AESIs) were identified, which are all discussed below:

Regarding the **cardiac events**, in the pivotal phase 3 study and pools 1 and 2, **major adverse cardiovascular events** (MACE) was defined as CV death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization, which corresponds to the definition for 'MACE-plus' as reflected in the *EMA Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)*, and can therefore be considered acceptable.
Overall, the number of oHCM patients who experienced MACE in the pivotal phase 3 study was low, with even a lower rate in the aficamten group (n=6, 4.2%) vs the placebo group (n=8, 5.7%). These MACE-plus consisted primarily of CV hospitalization (n=3, 2.1% aficamten vs n=4, 2.9% placebo) and non-fatal myocardial infarction (n=3, 2.1% aficamten vs n=5, 3.6% placebo), and were all considered isolated events. One participant in each treatment group had a non-fatal stroke. No participant died or had a cardiac arrest. Similar findings were shown in pool 1 (n=8, 4.7% aficamten vs n=9, 5.9% placebo). The incidence rate in pool 2 was 8.4%. Current data, including the exposure-adjusted incidence rates (EAIRs), do not provide concerns regarding MACE-plus, and the separate components within MACE, with the use of aficamten. However, the numbers are considered too low to draw firm conclusions. In this respect, as already indicated above, to exclude a detrimental effect on cardiovascular safety, the applicant is proposing a meta-analysis which was included as cat 3 study in the agreed RMP.

The occurrence of **ventricular tachyarrhythmia** in the pivotal phase 3 study was also low and even lower in the aficamten group compared to the placebo group, which is reassuring (n=2, 1.4% aficamten vs n=5, 3.6% placebo). These findings, including the EAIRs, were generally consistent in pools 1 and 2 and did, therefore, not point to a causal association of ventricular tachyarrhythmia AEs and the use of aficamten.

Regarding the AESI of **supraventricular tachyarrhythmia** (with focus on atrial fibrillation (AF)), 1 participant (0.7%) in each treatment group were reported with new onset persistent AF in the pivotal phase 3 study. In pool 1, a similar incidence rate was observed between groups (n=7, 4.1% aficamten vs n=6, 3.9% placebo) with AF (n=4, 2.4% aficamten vs n=5, 3.3% placebo) as the most frequently reported AE. Further, in pool 2, 26 participants (7.8%) had a supraventricular tachyarrhythmia event, of which 20 participants (6.0%) had AF. No concerns could be revealed from these data, including the EAIRs.

Hypertension occurred in the aficamten group more frequently than in the placebo group (n=11, 7.7% aficamten vs n=3, 2.1% placebo). Most of these patients had a history of hypertension, all cases were non-serious and there were no consequences on discontinuation of the drug use. This imbalance was also seen in pool 1 (n=11, 6.5% aficamten vs n=4, 2.6% placebo) and remained generally unchanged in pool 2 with 8.8%. Consistent with these findings, an increase in blood pressure (both systolic and diastolic) has been observed with the use of aficamten in oHCM patients and not in nHCM patients (see further discussion under section 'vital signs'). Overall, since a higher frequency in hypertension AEs and an increase in blood pressure has been observed in the aficamten group compared to the placebo group, since this imbalance cannot be exclusively explained by confounders and since the occurrence of these events may be explained by the mechanism of action, a causal relationship with the use of aficamten is likely. Therefore, hypertension has been added as an ADR to section 4.8 of the SmPC. Further, the applicant provided an additional explanation in the description of selected adverse reactions in section 4.8 of the SmPC to provide clinicians with adequate and clinically meaningful guidance.

In the pivotal phase 3 study, the percentages of subjects with **palpitations** was higher in the aficamten group (n=10, 7.0%) compared to placebo (n=4, 2.9%). This imbalance was also found in pool 1 (n=10, 5.9% aficamten vs n=5, 3.3% placebo), and the incidence rate remained consistent over time (pool 2, 8.7%). Therefore, palpitations has been addressedas an ADR in section 4.8 of the SmPC.

The frequency of **cardiac failure** AEs was lower in the aficamten group (n=8, 5.6%) compared to the placebo group (n=17, 12.1%) during the on-treatment period of the pivotal phase 3 study, which is re-assuring. However, the occurrence of cardiac failure was remarkably higher in the aficamten group during the washout period (n=14, 9.9% aficamten vs n=1, 0.7% placebo). The most frequently reported AEs during the washout period overall were dyspnoea and HCM (worsening symptoms). A similar trend was also seen in pool 1. This finding of a relatively higher incidence of cardiac failure AEs during the washout period could rather be explained by a withdrawal effect of aficamten.

The applicant performed also a special assessment on potential rebound symptoms (i.e. worsening of disease to levels worse than baseline after stopping treatment), where, in the pivotal phase 3 study, a notable disbalance was observed on CV AEs with an onset during the washout period in 23 participants on aficamten and 9 participants on placebo. Two participants on aficamten met the 3 criteria required for potential rebound. One subject experienced worsening HCM with symptoms of dyspnoea and palpitations 2 days after drug discontinuation and was ongoing at end of study (EOS), and 1 patient suffered also from dyspnoea and palpitations with no change in LVOT and NYHA class 6 days after drug discontinuation and was ongoing at EOS. Potential rebound symptoms, such as cardiac failure and

dyspnoea, when a patient decides to promptly discontinue treatment can be considered an important safety concern. This is currently adequately addressed in sections 4.2 and 4.4 of the SmPC.

Generally, **dizziness** is a common symptom in patients with oHCM. The incidence of the PT dizziness in the pivotal phase 3 study was low, but higher in the aficamten group (n=6, 4.2%) as compared to the placebo group (n=2, 1.4%). This imbalance of the incidence rate was also seen in pool 1 (n=11, 6.5% aficamten vs n=3, 2.0% placebo group). In pool 2, an AE rate was reported of 8.7%. Across all pools, no dizziness AE led to discontinuation of the study drug. Given this information,as an ADR to section 4.8 of the SmPC. Further, the applicant added an advice in section 4.7 of the SmPC that aficamten could influence the ability to drive and on the use of machines.

The **left ventricular ejection fraction** (LVEF) was used as the measure for systolic dysfunction, for which echocardiogram guided dosing has been introduced for aficamten. An exaggerated pharmacologic effect of reducing cardiac contractility by aficamten could lead to the risk of heart failure due to systolic dysfunction, which is defined by the applicant/investigator as LVEF<50% with or without symptoms.
In the pivotal phase 3 study, the mean LVEF values showed a decrease in the aficamten group, while LVEF values remained stable in the placebo group, which is not unexpected, based on the mechanism of action of aficamten. At week 24, the LS mean treatment difference vs placebo was −4.75% (95%CI: −6.27, −3.22; p<0.0001), and returned towards baseline (LS mean treatment difference vs placebo of −0.82% (95%CI: −2.09, 0.45; p=0.206) after stopping treatment.
Based on review of the site-assessed laboratory data in the pivotal phase 3 study, the incidence rate of patients with at least 1 LVEF value <50% (and a low incidence of LVEF <40%) was low, but higher in the aficamten group compared with the placebo group (n=7, 4.9% vs n=1, 0.7%, respectively). Nevertheless, there were no treatment interruptions and no associated signs or symptoms of heart failure, which is re-assuring. All aficamten-treated participants had a subsequent dose reduction (per protocol), and all participants had an LVEF ≥50% at the next visit, showing a positive de-challenge (reversible effect) pointing towards a causal association with the occurrence of the event and increase in aficamten dose. Data in pools 1 and 2 showed similar findings. Similar data were seen in the core laboratory data.
Therefore, systolic dysfunction, defined as "LVEF <50% with or without symptoms" has been included as an ADR in section 4.8 of the SmPC. Further, the safety concern 'heart failure due to systolic dysfunction' has been included as an important potential risk in the RMP.

Of note, the incidence of **muscle safety**, **syncope, stroke,** both acute and chronic **renal events** and **hepatic events** in the pivotal phase 3 study and the integrated analyses were low and generally balanced between groups. No safety concerns have been found from these data.

The incidence of **AEs leading to discontinuation** was very low and generally similar in the aficamten group (n=1, 0.7%) as compared with the placebo group (n=2, 1.4%) in the pivotal phase 3 study. Similar findings were observed with pools 1 (n=1, 0.6% aficamten vs n=2, 1.3% placebo) and 2, which included the same isolated case. Also no trend or pattern with respect to type of AE leading to drug interruptions has been identified.

The comparisons of the safety in **special populations** are only made in pool 1 of the integrated safety analysis, which can be considered acceptable.
Regarding **age**, **sex**, **race**, **eGFR, patients with or without a history of atrial fibrillation or flutter** and **background beta-blocker use** subpopulations, no new relevant safety concerns could have been identified from these data.

Further, no relevant effects from **ethnicity, NYHA class,** or **N-terminal Pro-B-Type natriuretic peptide** have been identified due to low numbers.

Regarding use in **pregnancy and lactation**, the performed non-clinical studies of aficamten are considered insufficient with respect to reproductive toxicity as described in Section 5.3 of the SmPC. There is no evidence from the use of aficamten in pregnant women. A careful benefit/risk evaluation is required before use and during pregnancy and MYQORZO should not be used during pregnancy unless the clinical condition of the woman requires treatment with aficamten.

Based on the mode of action of aficamten, a negative inotropic effect on the foetal heart cannot be ruled out. 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, also considering the maternal half-life of aficamten (approximately 4 days). Monitoring of the woman should consider the circulatory adaptations to pregnancy.

Based on the totality of evidence in non-clinical data, and the unmet medical need, the fact that a potential foetal harm cannot be ruled out, it was decided that although a contraindication in section 4.3 is not needed, a strict wording is proposed as discussed above for sections 4.4 and 4.6 of the SmPC. The safety concern of 'embryofetal toxicity' is included as important potential risk in the RMP, for which additional risk minimization measures are proposed.

No new relevant safety signals have been observed in the **overdose, medication errors** or **drug abuse** cases. No specific studies on the effects of mavacamten on the ability to drive or operate machinery have been performed, which is acceptable.

No clinically meaningful differences with respect to the **haematology** and **urinalysis parameters** and **clinical chemistry lab vales**, including liver function tests, have been observed for pools 1 and 2.

Regarding the **vital signs**, small increases on in systolic and diastolic BP were seen in the pivotal phase 3 study and pool 1 with the use of aficamten, as compared to placebo, and returned to baseline values during the washout period. However, the effect of aficamten use on BP in nHCM patients seems to be absent or lower, as compared to oHCM users, indicating that aficamten does not directly induce hypertension, but could be an effect of the relief of LVOT obstruction with subsequent improved cardiac output and an associated increase in arterial pressure (see discussion above on 'hypertension').
Also, the use of aficamten on **electrocardiograms** generally showed no significant effect in the pivotal phase 3 study. Postbaseline changes in these parameters were generally small and consistent between the aficamten and placebo groups. The data in pools 1 and 2 appeared to be consistent with those described for the phase 3 study. These data are in line with the findings in the phase 1 thorough QT study (CY 6019), which demonstrated that in healthy adults the studied single dose of 50 mg did not result in QTc prolongation (see clinical pharmacology section).

Of note, no relevant safety concerns have been observed from the overall presented safety data of pool 3 in the safety dossier.

2.6.10. Conclusions on the clinical safety

Aficamten is indicated for the treatment of symptomatic oHCM. The mechanism of action as a selective myosin inhibitor is reflected in observed LVEF reduction and associated symptoms which were more frequently reported in the aficamten group compared to in the placebo group. Aficamten appeared to be generally well tolerated with headache, palpitations and hypertension as most commonly reported AEs, and a potential rebound effect, when aficamten is discontinued. Gradual dose reduction may attenuate the rate of symptom recurrence following treatment discontinuation as recommended in the SmPC.

However, a detrimental effect on CV safety and embryofoetal toxicity could not be excluded and, therefore, remains of concern, which will be addressed post-marketing as reflected in agreed RMP.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 1. 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

2.7.2. Pharmacovigilance plan

Table 2. 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	<u>Primary objective:</u> To evaluate the incidence of heart failure from systolic dysfunction and/or severe systolic	Heart failure due to systolic dysfunction Long-term Safety,	First protocol submission: Interim study report:	Within 6 months of EC decision. Approximately one year after aficamten is commercially available for 2

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Hypertrophic Cardiomyopathy (oHCM) in Europe (Planned)	dysfunction in aficamten treated patients with symptomatic oHCM. <u>Secondary objective:</u> To evaluate the incidence of cardiovascular events and mortality in aficamten treated patients with symptomatic oHCM	including CV safety		years in the 3rd European Country.
			Study progress reports:	Included in PBRERs
			Final study report:	Within one year of the end of data collection.
CY 6022 A Follow-Up, Open-Label, Research Evaluation of Sustained Treatment with Aficamten (CK-3773274) 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	To assess aficamten cardiovascular safety based on endpoints of time to first occurrence of MACE	Heart failure due to systolic dysfunction	Protocol submission:	Within 90 days after EC decision
			Study progress reports:	Included in PBRERs

(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)	(cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular hospitalization) from randomization up to the end of study follow-up visit.		Final study report:	Completed within one year after approved protocol

2.7.3. Risk minimisation measures

Table 3. 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*	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*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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 and rifampicin* *PL sections 2, 3 and 4* **Additional risk minimization measures:** *HCP checklist* *Patient Card*	
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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Heart failure due to systolic dysfunction) *PL sections 2, 3, and 4* **Additional risk minimization measures:** *HCP checklist* *Patient Card*	Additional pharmacovigilance activities: *Study CY 6042* *Study CY 6022*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, MYQORZO (aficamten) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by left ventricular (LV) hypertrophy unexplained by other cardiac or systemic diseases. It is a chronic, progressive condition involving the cardiomyocyte and cardiac sarcomere, often familial, and is the most common genetic heart muscle disorder. Mutations in sarcomere proteins, such as cardiac myosin, increase calcium sensitivity, disrupt sarcomere structure, and enhance energy utilization, leading to hypercontractility, reduced LV compliance, smaller chamber size, supranormal ejection fraction, and diastolic dysfunction. Over time, HCM causes tissue remodelling with myocyte hypertrophy, disarray, microvascular changes, and fibrosis.

HCM is subclassified into obstructive (oHCM) and nonobstructive (nHCM) forms. Both exhibit LV hypercontractility, hypertrophy, and reduced compliance, but oHCM uniquely involves reduced LV outflow (gradient ≥30 mmHg) due to structural changes in the outflow tract. oHCM patients are at higher risk of progressive heart failure, systolic dysfunction, atrial fibrillation, and thromboembolic stroke. Symptoms include dyspnoea, fatigue, chest pain, and reduced exercise capacity, often worsening without treatment. Management focuses on lifestyle changes, medications, and septal reduction therapy to alleviate symptoms.

The aim of this new treatment, aficamten, which is a small molecule, is to inhibit cardiac myosin to reduce the hypercontractility that underlies the pathophysiology of HCM in the cardiac sarcomere. The reduction in cardiac contractile force is expected to alleviate LVOT obstruction in patients with oHCM by counteracting the excessive thickening of the left ventricular wall of the outflow tract.

The agreed indication for aficamten in the EU is as follows:

"MYQORZO is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1)."

3.1.2. Available therapies and unmet medical need

The European Society of Cardiology (ESC) guideline states that pharmacological therapy is administered on an empirical basis to improve functional capacity, reduce symptoms, and prevent disease progression. The current guideline relies on the use of established negative inotropic agents. Non-vasodilating beta-blockers (propranolol or nadolol) are recommended as first-line therapy in patients with symptomatic LVOT obstruction (Elliott et al. 2014 & Ommen et al. 2020). Calcium channel blockers (verapamil or diltiazem) are recommended in patients who are intolerant or have contra-indications to beta-blockers. Disopyramide is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil) if beta-blockers alone are ineffective. A combination of a beta-blocker and a calcium channel blocker is not recommended. However, none of the recommendations is supported by Level A Evidence, as the available clinical data are not supported by adequate, well-controlled, randomized, double-blind trials. Further, none of these medicinal products are approved for oHCM.

For patients with advanced symptomatic disease unresponsive to medications, septal reduction therapies (surgical myectomy or percutaneous alcohol ablation of the septum) can provide effective LVOT-G reduction (Elliott 2014; Gersh 2011; Ponikowski 2016). For those patients with HCM with end-stage disease who have both significant systolic impairment and diastolic dysfunction, cardiac transplantation may be the only treatment option (Gersh 2011).

Cardiac myosin inhibitors (CMIs) constitute a new class of drugs, that directly targets the underlying pathophysiology of HCM. The first-in-class CMI is mavacamten, which is approved for the treatment of symptomatic oHCM in the year 2023, and has been shown to improve symptoms and exercise capacity in patients with oHCM.

3.1.3. Main clinical studies

The main evidence of efficacy was a phase 3, randomized, placebo-controlled, double-blind, multi-centre trial CY 6031 in participants with oHCM, NYHA class II or III, an LVOT-G > 30 mmHg, LVEF ≥ 60% and a respiratory exchange ratio (RER) ≥1.05 and pVO2 ≤90% predicted on the screening CPET. A total of 282 eligible participants were included at 82 centres in 14 countries and were randomized in a 1:1 ratio to receive aficamten or placebo. Randomization was stratified by use of beta-blockers (yes or no) and cardiopulmonary exercise testing (CPET) exercise modality (treadmill or bicycle). During the initial 6 weeks of the treatment period, doses were individually titrated at weeks 2, 4, and 6 based on echocardiography-guided criteria. Dose escalation at weeks 2, 4, and 6 occurred only if a participant had a Valsalva LVOT-G ≥ 30 mmHg and a biplane left ventricular ejection fraction (LVEF) ≥ 55%. Echocardiograms were performed at each subsequent visit during the trial, and the dose was down-titrated if the LVEF was noted to be 40%-49%. The primary endpoint of peak oxygen uptake (pVO2) was measured by CPET at screening and at the end of treatment (Week 24). Secondary endpoints included change in KCCQ, change in SRT eligibility, improvement in NYHA classification and change in LVOT-G.

Supportive data were obtained from the placebo-controlled phase 2 study CY 6021 and the ongoing long-term open-label extension (OLE) study CY 6022.

The main source for the clinical safety evaluation was based on the pivotal phase 3 study CY 6031, supported by pooled data analyses. Pool 1 consisted of placebo-controlled data from the 24-weeks pivotal phase 3 study CY 6031 and the 10-weeks phase 2 dose-finding study CY2021. Pool 2 contained also longer term data from the OLE trial (CY2022).

3.2. Favourable effects

Primary endpoint of exercise capacity. The LS mean improvement in pVO2 by CPET from baseline to week 24 was 1.76 mL/kg/min (SD: 3.12) in the aficamten group and 0.02 mL/kg/min (SD: 2.73). The LS mean difference between treatment groups was 1.74 mL/kg/min (95% CI: 1.04, 2.44; p < 0.0001). This effect was consistent in sensitivity analyses and subgroup analyses.

Other (secondary) endpoints.
SRT eligibility- At baseline, 32 participants in the aficamten group and 29 participants in the placebo group were SRT eligible. Of these participants 4 (12.5%) in the aficamten group and 14 (48.3%) participants in the placebo group remained SRT eligible at Week 24. The common odds ratio (vs placebo) was 0.163 (95% CI: 0.031, 0.614; p = 0.005). During the 24-week treatment period,

aficamten treatment resulted in a significant reduction in the time spent SRT eligible by an LS mean of −78.1 days (95% CI: −99.8, −56.3; p < 0.0001) compared with placebo.
The aforementioned effect on SRT eligibility was not solely driven by one of the components (LVOT-G and NYHA) as aficamten had both an effect on LVOT-G (treatment difference vs placebo was −48 mmHg (95% CI: −55, −42; p < 0.0001)) and NYHA functional class improvement (odds ratio vs placebo for ≥ 1 improvement in NYHA class was 4.41 (95% CI: 2.56, 7.60; p < 0.0001)).

KCCQ-CSS

At week 24, 69 (48.6%) of the aficamten treated patients and 38 (27.1%) of the placebo treated patients had an improvement of ≥ 10 points in the KCCQ-CSS. The common odds ratio vs placebo for an improvement of ≥ 10 points in the KCCQ-CSS was 2.58 (1.52; 4.40); p < 0.001 in favor of aficamten. Using alternative cut-offs (5, 15, 20), comparable effects were found.

The LS mean change in KCCQ-CSS from baseline to Week 24 was 11.6 points in the aficamten group and 4.3 points in the placebo group. The LS mean difference between treatment groups of 7.3 points was statistically significant, favoring aficamten (95% CI: 4.6, 10.1; p < 0.0001).

Cardiac biomarkers

Treatment with aficamten resulted in significant decreases in the cardiac biomarkers hs-cTnI (-45%; p<0.0001) and NT-proBNP (-80%; p<0.0001) compared with placebo at week 24.

Cardiac magnetic resonance substudy. At Week 24, LV mass index, maximal LV septal wall thickness, maximal LV lateral wall thickness, and global LV max wall thickness all showed decreases from baseline in the aficamten group that were statistically significant compared to the changes observed in the placebo group.

3.3. Uncertainties and limitations about favourable effects

Long-term efficacy data. pVO_2max has only been assessed in the pivotal study CY-6031 and not the OLE CY-6022. Therefore, maintenance of effect on pVO_2max has not been demonstrated.
Preliminary data from the open-label extension provide support that the effects on SRT eligibility, NYHA classification improvement, LVOT-G and KCCQ-CSS were maintained up to week 120, albeit with a low sample size.

3.4. Unfavourable effects

Overall, available clinical safety data of treatment with aficamten with a minimum of 12 months can be considered sufficient with 198 aficamten-treated subjects with oHCM.

Adverse events (AEs) were balanced between treatment groups (73.9% aficamten vs 70.7% placebo). The most frequently reported AEs were headache (7.7% aficamten vs 7.1% placebo), hypertension (7.7% aficamten vs 2.1% placebo) and palpitations (7.0% aficamten vs 2.9% placebo). Results in pools 1 and 2 were generally comparable.

The incidence of **serious adverse events** (SAEs) was relatively low with even a lower rate in the aficamten group compared to the placebo group (5.6% vs 9.3%, respectively). The most frequent reported SAEs were HCM worsening of symptoms (2.1% aficamten vs 0.7% placebo) and atrial fibrillation (0.7% in each arm). Generally similar findings were seen in pools 1 and 2.

No **deaths** have been reported in the pivotal phase 3 trial and in pools 1 and 2.

Several **adverse events of special interest** (AESIs) were identified and discussed:
Regarding **cardiac events**, the incidence of **major adverse cardiovascular events** (MACE) was low, and was lower in the aficamten group (4.2%) vs the placebo group (6.4%), primarily consisting of CV hospitalization (2.1% aficamten vs 2.9% placebo) and non-fatal myocardial infarction (2.1% aficamten vs 4.3% placebo), and were all considered isolated events. One participant in each treatment group had a non-fatal stroke. No participant died or had a cardiac arrest. Similar findings were shown in pools 1 and pool 2.
Regarding the events of **ventricular tachyarrhythmia**, they were also lower in the aficamten group compared to the placebo group (1.4% aficamten vs 3.6% placebo), and findings were consistent in pools 1 and 2.
Further, the incidence of **supraventricular tachyarrhythmia**, **syncope** and **stroke** in the pivotal phase 3 study and the integrated analyses were low and generally balanced between groups. No safety concerns have been found from these data.
The **left ventricular ejection fraction** (LVEF) values showed a decrease in the aficamten group, while LVEF values remained generally stable in the placebo group, which is not unexpected based on the mechanism of action of aficamten. At week 24, the LS mean treatment difference vs placebo was −4.75% (95%CI: −6.27, −3.22; p<0.0001), and returned towards baseline (LS mean treatment difference vs placebo of −0.82% (95%CI: −2.09, 0.45; p=0.206) after stopping treatment. Also, a higher incidence rate of LVEF values <50% was seen with aficamten use (4.9% aficamten vs 0.7% placebo), but there were no treatment interruptions and no associated signs or symptoms of heart failure. All aficamten-treated participants had a subsequent dose reduction (per protocol), and all participants had an LVEF ≥50% at the next visit. Data in pools 1 and 2 showed a similar pattern.
'Systolic dysfunction, defined as LVEF <50% with or without symptoms' is included as an ADR in the SmPC and as an important risk in the RMP.
Furthermore, with continuous monitoring of the CV safety of aficamten by routine pharmacovigilance, and by a planned real world observational study, the applicant is proposing a meta-analysis (of CY 6031 and CY 6032) to allow an adequate evaluation of the CV safety profile of aficamten, according to the '*Reflection paper on assessment of cardiovascular safety profile of medicinal products*' (EMA/CHMP/50549/2015). This meta-analysis was added as category 3 study in the agreed version of the RMP.

A notable disbalance was observed on CV AEs with an onset **during the washout period** in 23 participants on aficamten and 9 participants on placebo, of whom, two participants on aficamten met the 3 criteria for **potential rebound effect**. This can be of concern, when a patient decides to promptly discontinue treatment. These points are currently sufficiently addressed in the SmPC where it was agreed that gradual dose reduction may attenuate the rate of symptom recurrence following treatment discontinuation.

Regarding **tolerability**, the incidence of AEs leading to discontinuation was very low and generally similar in the aficamten group (0.7%), as compared with the placebo group (1.4%) in the pivotal phase 3 study. Similar findings were observed with pools 1 and 2. Also no trend or pattern with respect to type of AE leading to drug interruptions has been identified.

Also, no safety signals with respect to the **haematology, clinical chemistry, cardiac biomarkers** and **urinalysis parameters** have been observed for pools 1 and 2.

3.5. Uncertainties and limitations about unfavourable effects

Regarding use in **pregnancy and lactation**, the performed non-clinical studies of aficamten were considered insufficient with respect to reproductive toxicity and foetal harm cannot be ruled out based on the mode of action of aficamten while currently no clinical safety data on pregnancy and lactation

are available. 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. Therefore, strict wording on the use of aficamten during pregnancy is agreed for the SmPC. Also, 'embryofetal toxicity' is included as important potential risk in the RMP for which additional risk minimization measures are proposed.

Regarding **DDIs**, aficamten is metabolized by predominantly by CYP2C9 and to lesser extent by CYP2D6, CYP2C19 and CYP3A enzymes. Patients who are stable on aficamten treatment and start with medications that inhibit CYP2C9 and other CYP enzymes (e.g., fluconazole, voriconazole, fluvoxamine, strong CYP2C9 inhibitors) increase aficamten plasma concentrations. This may increase the risk of heart failure due to systolic dysfunction. Dosing instructions for concomitant use of these medicines are agreed and implemented in the SmPC.

3.6. Effects Table

Table 4. Effects Table for aficamten for treatment of oHCM (data cut-off: December 2023).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in pVO2	LS mean change (SD) in pVO2 by CPET from baseline to Week 24.	mL/kg/min	1.76 (SD: 3.12)	0.02 (SD: 2.73)	Difference vs placebo is 1.74 (95% CI: 1.04; 2.44); P<0.001. **SoE**: Consistent across sensitivity and subgroup analyses.	CY 6031
SRT eligibility	Number of patients eligible for SRT at week 24	n at week 24 / n at baseline (%)	4/32 (12.5%)	14/29 (48.3%)	**SoE**: Aficamten resulted in reduction in the time spent SRT eligible (−78.1 days (95% CI: −99.8, −56.3; p < 0.0001)) Consistent effect on individual components of improvement NYHA classification to I or II and LVOT-G < 50 mmHg.	CY 6031
KCCQ-CCS responder analysis	Number of participants with ⩾ 10 points improvement at week 24	n (%)	69 (49%)	38 (27%)	Common odds ratio of 2.58 (95% CI: 1.52; 4.40); P<0.001. **SoE**: Responder analysis using 5, 15 or 20 as cut-off are comparable. Overall the LS mean difference in KCCQ-CSS between treatment groups is 7.3 points (95% CI: 4.6, 10.1; p < 0.0001).	CY 6031
Unfavourable Effects						
LVEF <50%	Left ventricle ejection fraction reduction to below <50%	n/N (%)	7/142 (4.9%)	1/140 (0.7%)	SoE: • LS mean treatment difference vs placebo: −4.75% (95%CI: −6.27, −3.22; p<0.0001), at week 24 • Similar data in pool 1 Unc: • Low numbers. • Limited long-term data.	CY 6031 CY 6021 CY 6022

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
MACE	Major adverse cardiovascular events defined as CV death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization	n/N (%)	6/142 (4.2%)	9/140 (6.4%)	SoE: • Similar data in pool 1 (4.7% aficamten vs 6.5% placebo). • Similar incidence rate in pool 2 (6.0%). Unc: • Low numbers. • Limited long-term data.	CY 6031 CY 6021 CY 6022

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current application is based on the results of a single pivotal study CY 6031, which is acceptable if the results are consistent and exceptionally compelling in terms of clinical relevance in line with *EMA Points to consider on application with 1. Meta-analyses, 2. One pivotal study (CPMP/EWP/2330/99)*. In study CY 6031, a statistically significant effect in exercise capacity measured by pVO_2max in oHCM patients administered aficamten compared with placebo was demonstrated (1.76 vs 0.02 ml/kg/min, respectively; p=<0.0001). Using internal and external data, the Applicant has supported the clinical relevance of this magnitude. Furthermore, internal validity has been shown in both a priori and post-hoc subgroup analyses, including history of atrial fibrillation and EU region.

Although a primary endpoint on morbidity and mortality would be preferred, it is acknowledged that such a trial is not feasible in the oHCM population, given the low prevalence and yearly mortality rates. According to the *EMA Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95, Rev.2)*, exercise capacity may be acceptable as a primary efficacy endpoint, in case the result is supported by secondary endpoints that meaningfully contribute to the understanding of the clinical relevance of the effect and the cardiovascular safety profile of the product can be adequately characterised. Treatment with aficamten resulted in beneficial effects in the most relevant secondary endpoints of the number of participants eligible for septal reduction therapy (SRT) after 24 weeks (4 (12.5%) vs 14 (48.3%) in the aficamten and placebo group, respectively) and duration spent eligible for SRT (-78.1 days compared with placebo). Although this endpoint only focussed on eligibility and not on actual number of participants on waiting lists and having SRT performed, the endpoint remains of importance, since SRT is clinically relevant to patients and clinicians as it is a highly invasive surgery associated with significant consequential risk. Additional analyses demonstrated that this effect was not driven by either reduction in LVOT-G or improvement of NYHA classification alone, as effects on both secondary endpoints were found.

Furthermore, the beneficial effect on exercise capacity (pVO2max) and preventing patients from (progressing to) septal reduction therapy eligibility is supported by significant improvements in quality of life, measured using responder analyses of patients improving more than 10 points in KCCQ-CSS (48.6% vs 27.1%) and the continuous analyses of change from baseline (11.6 vs 4.3 points).

Lastly, supportive data demonstrated that aficamten led to significant reductions in cardiac biomarkers (NT-proBNP and cardiac troponin I) and improved cardiac structure in a MRI substudy.

Since the efficacy endpoint pVO2 max was not included in the open label-phase, uncertainty remains regarding the maintenance of effect on this endpoint. However, the effects on secondary endpoints appeared to be persistent up to week 120, albeit with a low sample size.

Clinical safety data are primarily based on the pivotal phase 3 study CY 6031, supported by an integrated (pooled) safety data analysis (i.e. pool 1 with placebo-controlled data, and pool 2 consisting of longer term data). Aficamten appeared to be generally well tolerated with a comparable pattern of AEs between treatment groups, with headache, palpitations and hypertension as the most common reported AEs, and with a low frequency of discontinuations, which is re-assuring. Furthermore, no important safety signals, also with regard to CV safety, have been identified during aficamten therapy. However, a detrimental effect on long-term safety including CV safety could not be excluded and therefore remains of concern, is included as missing information in the RMP and will be addressed

post-marketing as part of additional pharmacovigilance activities. In the non-clinical data, embryo-fetal toxicity is included as important potential risk in the agreed RMP and will also be addressed by routine and additional risk minimization measures.

3.7.2. Balance of benefits and risks

The benefits of aficamten in terms of significant improvement in exercise capacity as measured by an improvement in pVO_2max compared to placebo and a reduced need for septal reduction therapy in patients with oHCM who received aficamten compared with placebo are accompanied by limited risks as aficamten appeared to be generally well tolerated with a comparable pattern of AEs between treatment groups. For important identified risk (heart failure due to systolic dysfunction and embryofoetal toxicity) additional risk minimisations measures are agreed.

The agreed indication for MYQORZO is in line with previous wordings of the indications within the same therapeutic area with aficamten being another cardiac myosin inhibitor for treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).

3.7.3. Additional considerations on the benefit-risk balance

Patient and healthcare provider engagement

The results of the interviews with six patients of the patient organisation European Heart Network (EHN) and the findings of the interview with the healthcare professionals' (HCP) of the European Society of Cardiology (ESC) show insight on the patient's quality of life and the HCP's view on current therapies and its advantages and disadvantages.

The patient's quality of life is generally good, but they have restricted or limited physical abilities. They are not willing to accept more side-effects of their medication, than they currently have.

The HCP's interview shows that there are currently clear recommendations for the treatment of oHCM, as stated in the ESC guidelines, including the treatment with another cardiac myosin inhibitor (MCI), mavacamten, which has demonstrated to be tolerable, and requires several safety precautions.

3.8. Conclusions

The overall benefit/risk balance of MYQORZO is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of MYQORZO is favourable in the following indication(s):

MYQORZO is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

The educational programme is aimed to educate Healthcare Professionals (HCPs) and patients on the important potential risk of heart failure due to systolic dysfunction and embryo-foetal toxicity.

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 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 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 arrythmia, dyspnoea, chest pain, fatigue or leg oedema.
- Check that the patient is not currently planning on taking fluconazole or rifampicin while taking aficamten.
- Assess for potential 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 of foetal cardiac functions.
- Ensure the patient is closely monitored; consider 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 (e.g. severe infection), new arrhythmia (e.g. new or uncontrolled atrial fibrillation or other uncontrolled tachyarrhythmia), assess for worsening systolic function.
- Remind the patient 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 a CYP2C9 inhibitor or discontinue 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.

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, or serious infection.
- Instruction not to start, stop or change any medicine without consulting the prescriber of aficamten.

Contact details of the prescriber.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Aficamten is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0123/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.