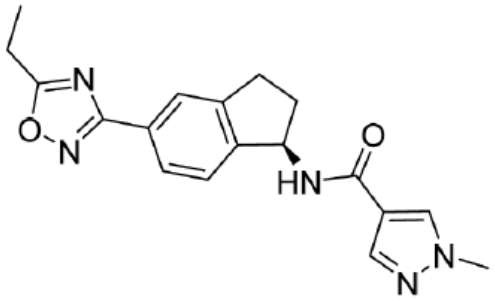
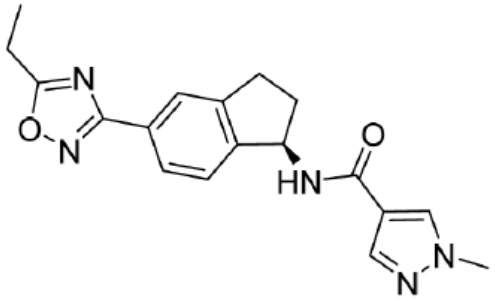
There is a need for treatments that improve exercise capacity, compared with a beta blocker, in both recently diagnosed and chronic symptomatic oHCM patients.

BRIEF SUMMARY

[0005] Methods and compositions for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM), comprising administering a cardiac myosin inhibitor aficamten, or a pharmaceutically acceptable salt thereof, are described herein. In some examples, the present disclosure provides methods for improving exercise capacity in a patient, e.g., a patient suffering from oHCM, comprising administering or delivering to the patient aficamten, or a pharmaceutically acceptable salt thereof as described herein. In some examples, the present disclosure provides methods for reducing symptom burden, improving hemodynamics, and improving exercise capacity in a patient, e.g., a patient suffering from oHCM, comprising administering or delivering to the patient aficamten, or a pharmaceutically acceptable salt thereof as described herein. In one aspect, the present disclosure refers to use of aficamten

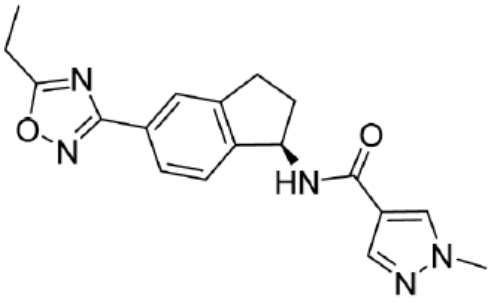


(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for improving myocardial mechanics or global longitudinal strain (GLS) in a patient in need thereof, wherein the patient has obstructive hypertrophic cardiomyopathy (oHCM). The methods disclosed herein may be useful for treating patients who have been recently diagnosed with oHCM (diagnosed within 12 months prior to administering aficamten, or a pharmaceutically acceptable salt thereof). In one aspect, the present disclosure refers to use of aficamten

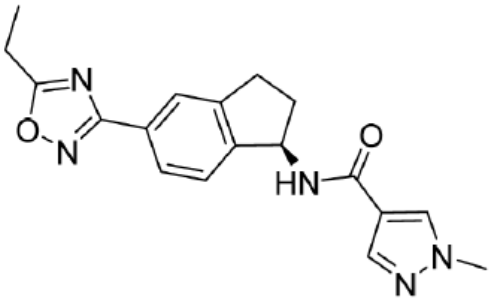


(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein the patient has been diagnosed with oHCM within 12 months before aficamten, or a pharmaceutically acceptable salt thereof, is to be administered. Patients who have been recently diagnosed with oHCM may include patients that are treatment naïve, and patients who have been treated or are being treated with a standard of care (SOC) medical therapy for oHCM. The methods disclosed herein may be useful for treating patients who are treatment naïve (not yet treated

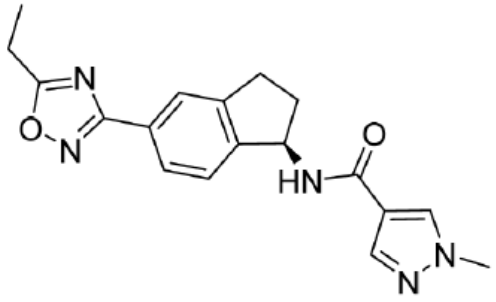
for oHCM). In another aspect, the present disclosure refers to use of aficamten



(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein the patient is treatment naïve for oHCM. The methods disclosed herein may be useful for treating patients with chronic oHCM. Patients with chronic oHCM include patients with a history of oHCM >12 months who are currently being treated with SOC therapy for oHCM, or who have received SOC therapy for oHCM within 12 months prior to administering aficamten, or a pharmaceutically acceptable salt thereof. SOC therapies include treatment of oHCM comprising administration of a beta-blocker, a calcium channel blocker, or disopyramide. In one aspect, the present disclosure refers to use of aficamten

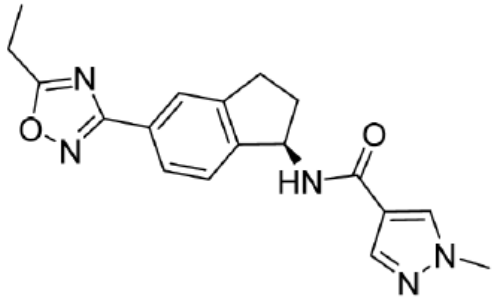


(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein: (1) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered in combination with a first dose of a standard-of-care therapeutic for oHCM, for a first time period; and (2) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered in combination with a second dose of the standard-of-care therapeutic for oHCM, for a second time period, wherein the second dose of the standard-of-care therapeutic for oHCM is lower than the first dose of the standard-of-care therapeutic. In another aspect, the present disclosure refers to use of aficamten

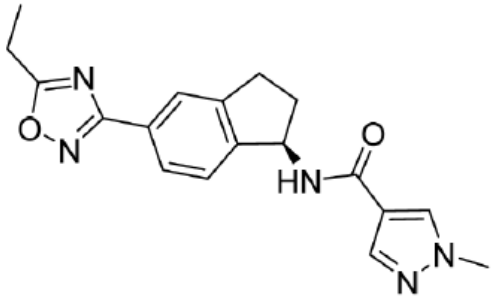


(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein: (1) a background therapy comprising at least one standard-of-care therapeutic selected from the group consisting of beta blockers, non-dihydropyridine calcium channel blockers, and disopyramide, is to be administered; (2) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered in combination with the background therapy, for a first time period; and (3) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered in combination with a second dose of the standard-of-care therapeutic for oHCM, for a second time period, wherein the second dose of the standard-of-care therapeutic for oHCM is lower than the first dose of the standard-of-care therapeutic.

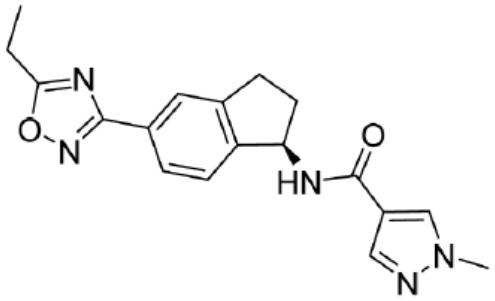
[0006] In some examples of the methods disclosed herein, the methods comprise administering aficamten, or a pharmaceutically acceptable salt thereof, as a monotherapy for oHCM. It is to be understood that administering a monotherapy for oHCM indicates that the patient only receives one therapy (e.g., aficamten, or a pharmaceutically acceptable salt thereof) for the treatment of oHCM; however, it is to be understood that the patient may also receive other therapy or therapies for the treatment of other diseases. As described herein, "other therapy or therapies for the treatment of other diseases" excludes SOC therapies for oHCM (e.g., one or more of a beta-blocker, a calcium channel blocker, or disopyramide). In one aspect, the present disclosure refers to use of aficamten



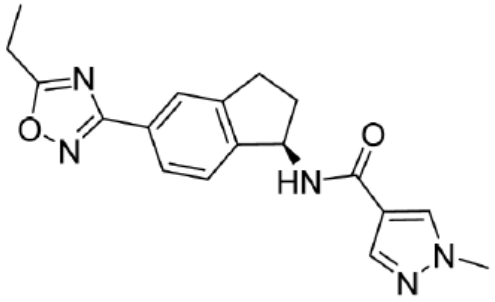
(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein aficamten, or the pharmaceutically acceptable salt thereof, is to be administered as a monotherapy for oHCM, and wherein the patient has chronic oHCM and has previously received standard of care medical therapy for oHCM and has discontinued said therapy before aficamten, or a pharmaceutically acceptable salt thereof, is to be administered. In another aspect, the present disclosure refers to use of aficamten



(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein the patient is receiving one or more background therapies for oHCM and at least one background therapy is to be reduced and/or stopped. In another aspect, the present disclosure refers to use of aficamten



(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein: (1) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered in combination with a standard-of-care therapeutic for oHCM, for a first time period; and (2) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered as a monotherapy, for a second time period. In yet another aspect, the present disclosure refers to use of aficamten



(aficamten), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein: (1) a background therapy comprising at least one standard-of-care therapeutic selected from the group consisting of beta blockers, non-dihydropyridine calcium channel blockers, and disopyramide, is to be administered; (2) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered in combination with the background therapy, for a first time period; and (3) aficamten, or a pharmaceutically acceptable salt thereof, is to be administered as a monotherapy, for a second time period. As

further described herein, the daily dose of aficamten may be titrated based on the results of an echocardiogram.

[0007] In some examples of the methods disclosed herein, the patient has one or more of the following prior to administering aficamten, or a pharmaceutically acceptable salt thereof: LVEF ≥ 60%; resting LVOT-G ≥ 30 mm Hg; post-Valsalva LVOT-G ≥ 50 mmHg; NYHA Class II or Class III. In some examples, a patient has pVO_2 <80%. In some examples, a patient has a predicted pVO_2 <80%. In some examples, a patent has a resting LVOT-G ≥30 mmHg, post-Valsalva peak LVOT-G ≥50 mmHg, is characterized as being in NYHA functional class II or III, and has a pVO_2 <80% (measured or predicted).

[0008] In some examples of the methods disclosed herein, administration with aficamten, or a pharmaceutically acceptable salt thereof, results in an improvement in one or more of: exercise capacity; heart function as measured by improvement in NYHA Functional Classification; resting LVOT-G; post-Valsalva LVOT-G; health status as measured by Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS); structural remodeling as measured by reduction in one or more of mean left ventricular mass index (LVMI) and left atrial volume index (LAVI); N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels; high sensitivity cardiac troponin I (hs-cTnI) levels; diastolic function as measured by reduction in lateral E/e'; interventricular septal thickness remodeling, as measured by change in interventricular septal thickness (IVST); CPET parameters selected from: ventilatory efficiency/carbon dioxide production (VE/VCO2 slope), circulatory power (VO2 × systolic blood pressure), ventilatory anaerobic threshold (VAT), total workload (watts), and heart rate response; and health status and health-related quality of life as measured by patient-reported outcome (PRO) questionnaires EuroQol 5 dimension 5-level instrument (EQ-5D-5L), Clinical Global Impression (CGI), Patient Global Impression of Change (PGI-C), and Seattle Angina Questionnaire-7 (SAQ-7). In some examples of the methods disclosed herein, administration with aficamten, or a pharmaceutically acceptable salt thereof, results in an improvement in one or more of: exercise capacity; heart function as measured by improvement in NYHA Functional Classification; resting LVOT-G; post-Valsalva LVOT-G; health status as measured by Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS); structural remodeling as measured by reduction in one or more of mean left ventricular mass index (LVMI) and left atrial volume index (LAVI); N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels; high sensitivity cardiac troponin I (hs-cTnI) levels; diastolic function as measured by reduction in lateral E/e'; interventricular septal thickness

remodeling, as measured by change in interventricular septal thickness (IVST); CPET parameters selected from: ventilatory efficiency/carbon dioxide production (VE/VCO2 slope), circulatory power (VO2 × systolic blood pressure), ventilatory anaerobic threshold (VAT), total workload (watts), and heart rate response; and health status and health-related quality of life as measured by patient-reported outcome (PRO) questionnaires EuroQol 5 dimension 5-level instrument (EQ-5D-5L), Clinical Global Impression (CGI), Patient Global Impression of Change (PGI-C), Seattle Angina Questionnaire-7 (SAQ-7), and Short-Form Survey (SF-36). In some examples, the one or more improved results are improved as compared to treatment with a SOC therapy (e.g., metoprolol). In some examples administration with aficamten, or a pharmaceutically acceptable salt thereof, results in an improvement in HCM symptoms, such as reductions of chest pain, dizziness, shortness of breath, fainting during physical activity, tiredness, low energy, limitations in physical activity.

[0009] A method of treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, can include administering to the patient a therapeutically effective amount of aficamten, or a pharmaceutically acceptable salt thereof, wherein the therapeutically effective amount of aficamten, or a pharmaceutically acceptable salt thereof, is selected by titrating a daily dose of aficamten, or a pharmaceutically acceptable salt thereof, administered to the patient. In some examples, the dose is titrated once during a course of treatment. In some examples, the dose is titrated two or more times during a course of treatment. The daily dose may be administered to a patient at a constant amount for about two weeks before the daily dose amount is titrated.

[0010] In some examples of the above methods, aficamten, or a pharmaceutically acceptable salt thereof is administered at a daily dose of about 5 mg to about 20 mg. In some examples, the daily dose is about 5 mg. In some examples, the daily dose is about 10 mg. In some examples, the daily dose is about 15 mg. In some examples, the daily dose is about 20 mg. For example, as described herein, in some examples, patients begin with 5 mg once daily; at about weeks 2, 4, and 6 patients receive an echocardiogram to determine if they will be up-titrated to doses of 10, 15 or 20 mg; and dose escalation will occur if a patient has a post-Valsalva LVOT-G ≥30 mmHg and a biplane left ventricular ejection fraction (LVEF) ≥55%, and patients who do not meet escalation criteria will continue to receive their current dose or may be down-titrated if their LVEF is below 50%. See, e.g., Table 26 for increasing, maintaining, reducing or discontinuing doses. As appreciated by those skilled in the art and described herein, unless indicated otherwise,

amount, e.g., in a dose, is of the amount of aficamten free base or the corresponding amount of aficamten free base when a non-free base form, e.g., a pharmaceutically acceptable salt, is administered.

[0011] In some examples, the daily dose is administered as a single dose each day. In some examples, the daily dose is administered in 2 divided doses.

[0012] In some examples, a method of treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, comprises: administering to the patient a first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a first time period; and based on one or more components of a first echocardiogram for the patient acquired after the first time period, administering to the patient a second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a second time period or terminating the administering of aficamten, or a pharmaceutically acceptable salt thereof, to the patient. The method may include selecting the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, based on the one or more components of the first echocardiogram. In some examples, the one or more components of the first echocardiogram comprises a biplane LVEF, or a biplane LVEF and a post-Valsalva LVOT-G. In some examples, the one or more components of the first echocardiogram comprises a biplane LVEF. In some examples, the one or more components of the first echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G. In some examples of the methods described herein, the patient undergoes two or more echocardiograms within the first time period, and the second daily dose is selected based on the combined results of two or more echocardiograms obtained within the first time period.

[0013] In some examples of the above methods, the one or more components of the first echocardiogram comprises a biplane LVEF, and the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is lower than the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is below a predetermined biplane LVEF threshold. For example, the predetermined biplane LVEF threshold may be 50%.

[0014] In some examples of the above methods, the one or more components of the first echocardiogram comprises a biplane LVEF, and the administering of aficamten, or a pharmaceutically acceptable salt thereof, to the patient is terminated when the biplane LVEF of the first echocardiogram is below a predetermined biplane LVEF threshold. For example, the predetermined biplane LVEF threshold may be 50%.

[0015] In some examples of the above methods, the one or more components of the first echocardiogram comprises a biplane LVEF, and wherein the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is at or above the predetermined biplane LVEF threshold and below a second predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 50%, and the second predetermined biplane LVEF threshold is 55%.

[0016] In some examples of the above methods, the one or more components of the first echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G, and wherein the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is at or above a second predetermined biplane LVEF threshold, and the post-Valsalva LVOT-G of the first echocardiogram is below a predetermined post-Valsalva LVOT-G threshold. In some examples, the second predetermined biplane LVEF threshold is 55%, and the predetermined post-Valsalva LVOT-G threshold is 30 mmHg.

[0017] In some examples of the above method, the one or more components of the first echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G, and wherein the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is at or above the predetermined post-Valsalva LVOT-G threshold. In some examples, the predetermined biplane LVEF threshold is 55%, and the post-Valsalva LVOT-G threshold is 30 mmHg.

[0018] In some examples of the above methods, the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg of aficamten. In some examples, the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of aficamten. In some examples of the above method, the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg of aficamten and the second is about 10 mg of aficamten.

[0019] In some examples of the above methods, the method further comprises measuring the one or more components of the first echocardiogram.

[0020] In some examples of the above methods, first time period is about 2 weeks. In some examples, the second time period is about 2 weeks. For example, as described herein, in some examples, a provided method comprises:

administering to a patient a first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a first time period, wherein the first daily dose is about 5 mg of aficamten and the first time period is about 2 weeks;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the first time period; and

if the patient has a post-Valsalva LVOT-G ≥30 mmHg and LVEF ≥55%, administering to the patient a second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, wherein the second daily dose is about 10 mg of aficamten; and if the patient has a post-Valsalva LVOT-G <30 mmHg or LVEF <55%, administering to the patient a second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, wherein the second daily dose is about 5 mg of aficamten.

As described herein, in some examples, a second daily dose is administered for a second time period (e.g., about 2 weeks) before a patient is assessed for post-Valsalva LVOT-G and LVEF.

[0021] In some examples of the above methods, the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is administered to the patient for the second time period, and the method further comprises, based on one or more components of a second echocardiogram for the patient acquired after the second time period and the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, administering to the patient a third daily dose of aficamten, or a pharmaceutically acceptable salt thereof for a third time period or terminating the administering of aficamten, or a pharmaceutically acceptable salt thereof to the patient. In some examples, the method comprises selecting the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, based on the one or more components of the second echocardiogram and the second daily dose. In some examples, the one or more components of the second echocardiogram comprises a biplane LVEF or a post-Valsalva LVOT-G. In some examples, the one or more components of the second echocardiogram comprises a biplane LVEF. In some examples, the one or more components of the second echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G. In some examples of the methods described herein, the patient undergoes two or more echocardiograms within the second time period, and the third daily dose is selected

based on the combined results of two or more echocardiograms obtained within the second time period.

[0022] In some examples of the above methods, the one or more components of the second echocardiogram comprises a biplane LVEF, and the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is lower than the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, or the administering of aficamten, or a pharmaceutically acceptable salt thereof, to the patient is terminated, when the biplane LVEF of the second echocardiogram is below the predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 50%.

[0023] In some examples of the above methods, the administering of aficamten, or a pharmaceutically acceptable salt thereof, to the patient is terminated when the biplane LVEF of the second echocardiogram is below the predetermined biplane LVEF threshold and the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof is the same as the first daily dose of aficamten or lower. In some examples, the predetermined biplane LVEF threshold is 50%.

[0024] In some examples of the above methods, the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is lower than the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the second echocardiogram is below the predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 50%. In some examples, the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof.

[0025] In some examples of the above methods, the one or more components of the second echocardiogram comprises a biplane LVEF, and wherein the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF is at or above the predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 50%, the second predetermined biplane LVEF threshold is 55%, and the second predetermined post-Valsalva LVOT-G threshold is 30 mmHg.

[0026] In some examples of the above methods, the one or more components of the second echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G, and

wherein the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is below the predetermined post-Valsalva LVOT-G threshold. In some examples, the second predetermined biplane LVEF threshold is 55%, and the predetermined post-Valsalva LVOT-G threshold is 30 mmHg.

[0027] In some examples of the above methods, the one or more components of the second echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G, and wherein the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the second echocardiogram is above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G of the second echocardiogram is at or above the predetermined post-Valsalva LVOT-G threshold. In some examples, the second predetermined biplane LVEF threshold is 55%, and the predetermined post-Valsalva LVOT-G threshold is 30 mmHg.

[0028] In some examples of the above method, the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg of aficamten, the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of aficamten, and the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of aficamten. For example, as described herein, in some examples, a provided method comprises:

administering to the patient a daily dose of aficamten, or a pharmaceutically acceptable salt thereof (may be referred to as a second daily dose), for a time period (may be referred to as a second time period), wherein the daily dose is about 10 mg of aficamten and the time period is about 2 week;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the time period; and

if the patient has a post-Valsalva LVOT-G ≥30 mmHg and LVEF ≥55%, administering to the patient a daily dose of aficamten, or a pharmaceutically acceptable salt thereof (may be referred to as a third daily dose), wherein the daily dose is about 15 mg of aficamten; and if the patient has a post-Valsalva LVOT-G <30 mmHg or LVEF <55%, administering to the patient a daily dose of aficamten, or a pharmaceutically acceptable salt thereof (may be referred to as a third daily dose), wherein the daily dose is about 10 mg of

aficamten (e.g., LVEF ≥50%) or about 5 mg of aficamten (e.g., LVEF <50% but ≥40%), or discontinuing administration for a period of time if LVEF is <40%.

For example, in some examples, a provided method comprises:

administering to a patient a first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a first time period, wherein the first daily dose is about 5 mg of aficamten and the first time period is about 2 weeks;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the first time period, wherein the patient has a post-Valsalva LVOT-G ≥30 mmHg and LVEF ≥55%;

administering to the patient a second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a second time period, wherein the second daily dose is about 10 mg of aficamten and second time period is about 2 week;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the second time period; and

if the patient has a post-Valsalva LVOT-G ≥30 mmHg and LVEF ≥55%, administering to the patient a third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, wherein the third daily dose is about 15 mg of aficamten; and if the patient has a post-Valsalva LVOT-G <30 mmHg or LVEF <55%, administering to the patient a third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, wherein the third daily dose is about 10 mg of aficamten (e.g., LVEF ≥50%) or about 5 mg of aficamten (e.g., LVEF <50% but ≥40%), or discontinuing administration for a period of time if LVEF is <40%.

As described herein, in some examples, a third daily dose is administered for a third time period (e.g., about 2 weeks) before a patient is assessed for post-Valsalva LVOT-G and LVEF.

[0029] In some examples of the above methods, the method further comprises measuring the one or more components of the second echocardiogram.

[0030] In some examples of the above methods, the third time period is about 2 weeks.

[0031] In some examples of the above methods, the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is administered to the patient for the third time period, the method further comprising, based on one or more components of a third echocardiogram for the patient acquired after the third time period and the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, administering to the patient a fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a fourth time period or terminating the administering of aficamten, or a pharmaceutically acceptable salt thereof,

to the patient. In some examples, the method further comprises selecting the fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, based on the one or more components of the third echocardiogram and the third daily dose. In some examples, the one or more components of the third echocardiogram comprises a biplane LVEF or a post-Valsalva LVOT-G. In some examples, the one or more components of the third echocardiogram comprises a biplane LVEF. In some examples, the one or more components of the third echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G. In some examples of the methods described herein, the patient undergoes two or more echocardiograms within the third time period, and the fourth daily dose is selected based on the combined results of two or more echocardiograms obtained within the third time period.

[0032] In some examples of the above methods, the one or more components of the third echocardiogram comprises a biplane LVEF, and the fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is lower than the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, or the administering of aficamten, or a pharmaceutically acceptable salt thereof, to the patient is terminated, when the biplane LVEF of the third echocardiogram is below the predetermined biplane LVEF threshold. In some examples, the administering of aficamten, or a pharmaceutically acceptable salt thereof, to the patient is terminated when the biplane LVEF of the third echocardiogram is below the predetermined biplane LVEF threshold and the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof. In some examples, the predetermined biplane LVEF threshold is 50%.

[0033] In some examples of the above methods, the one or more components of the third echocardiogram comprises a biplane LVEF, and wherein the fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF is at or above the predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 50%, the second predetermined biplane LVEF threshold is 55%.

[0034] In some examples of the above methods, the one or more components of the third echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G, and wherein the fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the

biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is below the predetermined post-Valsalva LVOT-G threshold. In some examples, the second predetermined biplane LVEF threshold is 55%, and the second predetermined post-Valsalva LVOT-G threshold is 30 mmHg.

[0035] In some examples of the above methods, the one or more components of the third echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G, and wherein the fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the third echocardiogram is above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G of the third echocardiogram is at or above the predetermined post-Valsalva LVOT-G threshold. In some examples, the second predetermined biplane LVEF threshold is 55%, and the second predetermined post-Valsalva LVOT-G threshold is 30 mmHg.

[0036] In some examples of the above methods, the first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg of aficamten, the second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of aficamten, the third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of aficamten, and the fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, about 15 mg, or about 20 mg of aficamten. For example, as described herein, in some examples, a provided method comprises:

administering to the patient a daily dose of aficamten, or a pharmaceutically acceptable salt thereof (may be referred to as a third daily dose), for a time period (may be referred to as a third time period), wherein the daily dose is about 15 mg of aficamten and the time period is about 2 week;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the time period; and

if the patient has a post-Valsalva LVOT-G ≥30 mmHg and LVEF ≥55%, administering to the patient a daily dose of aficamten, or a pharmaceutically acceptable salt thereof (may be referred to as a fourth daily dose), wherein the daily dose is about 20 mg of aficamten; and if the patient has a post-Valsalva LVOT-G <30 mmHg or LVEF <55%, administering to the patient a daily dose of aficamten, or a pharmaceutically acceptable salt thereof (may be referred to as a fourth daily dose), wherein the daily dose is about 15 mg of

aficamten (e.g., LVEF ≥50%) or about 10 mg of aficamten (e.g., LVEF <50% but ≥40%), or discontinuing administration for a period of time if LVEF is <40%.

For example, in some examples, a provided method comprises:

administering to a patient a first daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a first time period, wherein the first daily dose is about 5 mg of aficamten and the first time period is about 2 weeks;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the first time period, wherein the patient has a post-Valsalva LVOT-G ≥30 mmHg and LVEF ≥55%;

administering to the patient a second daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a second time period, wherein the second daily dose is about 10 mg of aficamten and second time period is about 2 week;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the second time period; and

administering to the patient a third daily dose of aficamten, or a pharmaceutically acceptable salt thereof, for a third time period, wherein the third daily dose is about 15 mg of aficamten and third time period is about 2 week;

assessing post-Valsalva LVOT-G and LVEF of the patient (e.g., using echocardiogram) after the third time period; and

if the patient has a post-Valsalva LVOT-G ≥30 mmHg and LVEF ≥55%, administering to the patient a fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, wherein the third daily dose is about 20 mg of aficamten; and if the patient has a post-Valsalva LVOT-G <30 mmHg or LVEF <55%, administering to the patient a fourth daily dose of aficamten, or a pharmaceutically acceptable salt thereof, wherein the fourth daily dose is about 15 mg of aficamten (e.g., LVEF ≥50%) or about 10 mg of aficamten (e.g., LVEF <50% but ≥40%), or discontinuing administration for a period of time if LVEF is <40%..

As described herein, in some examples, a fourth daily dose is administered for a fourth time period (e.g., about 2 weeks) before a patient is assessed for post-Valsalva LVOT-G and LVEF. In some examples, a fourth daily dose is administered for about 2 or more weeks, e.g., about 4 weeks, about 1 month, about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months, or longer. In some examples, during a fourth time period, e.g., a fourth time period longer than about 2 weeks, a patient may be assessed one or more times for cardiac structures and/or

functions, e.g., post-Valsalva LVOT-G, LVEF, exercise capacity, etc. As described herein, among other things, provided methods can improve exercise capacity.

[0037] In some examples of the above methods, the method further comprises measuring the one or more components of the third echocardiogram.

[0038] In some examples of the above methods, the fourth time period is about 2 weeks.

[0039] In some examples of the above methods, the first predetermined biplane LVEF threshold is 50%, the second predetermined biplane LVEF threshold is 55%, and the predetermined post-Valsalva LVOT-G threshold is 30 mmHg.

[0040] In some examples, a daily dose is about 15 mg of aficamten. In some examples, a third daily dose is about 15 mg of aficamten. In some examples, a fourth daily dose is about 15 mg of aficamten. In some examples, a daily dose is about 20 mg of aficamten. In some examples, a fourth daily dose is about 20 mg of aficamten. In some examples, a daily dose is administered as a tablet. In some examples, amount of aficamten, which may exist in multiple forms (e.g., free form, pharmaceutically acceptable salt forms, polymorph forms, etc.), in a tablet is about a daily dose as described herein. In some examples, the amount of aficamten in a tablet is about 5 mg. In some examples, the amount of aficamten in a tablet is about 10 mg. In some examples, the amount of aficamten in a tablet is about 15 mg. In some examples, the amount of aficamten in a tablet is about 20 mg. In some examples, the amount of aficamten in a tablet is about half of a daily dose as described herein. In some examples, the amount of aficamten in a tablet is about 2.5 mg. In some examples, the amount of aficamten in a tablet is about 5 mg. In some examples, the amount of aficamten in a tablet is about 7.5 mg. In some examples, the amount of aficamten in a tablet is about 10 mg.

[0041] In some examples of any of the above methods, the aficamten or pharmaceutically acceptable salt thereof is administered orally. In some examples, the aficamten or pharmaceutically acceptable salt thereof is administered as a tablet. In some examples, the tablet comprises one or more carriers or excipients selected from the group consisting of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium croscarmellose, glucose, gelatin, sucrose, and magnesium carbonate. In some examples, the tablet comprises: (i) about 1 % by weight to about 50 % by weight of the aficamten or pharmaceutically acceptable salt thereof; (ii-1) about 10 % by weight to about 60 % by weight of mannitol; (ii-2) about 5 % by weight to about 45 % by weight of microcrystalline cellulose; (iii) about 0.1 % by weight to about 10 % by weight of hydroxypropyl cellulose; (iv) about 1 % by weight to about 10 % by weight of croscarmellose sodium; (v) about 0.1 %

by weight to about 10 % by weight of sodium lauryl sulfate; and vi) about 0.1 % by weight to about 10 % by weight of magnesium stearate, wherein the % by weight excludes the weight of a coating, if present. In some examples, the aficamten or pharmaceutically acceptable salt thereof comprises polymorphic one or more of Form I, Form II, Form III, Form IV, Form V, and Form VI of aficamten.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] FIG. 1 illustrates and exemplary method for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient that included titrating the daily dose of aficamten, or a pharmaceutically acceptable salt thereof.

[0043] FIG. 2 shows a schematic overview of a phase 1 clinical study for aficamten. The study included SAD cohorts, MAD cohorts, a CYP2D6-PM cohort, and a food-effect cohort. The MAD and CYP2D6-PM cohorts began when a tolerated, pharmacologically active dose (reduction in LVEF of approximately 5%) was identified in the SAD cohorts. The food-effect cohort began following completion of the last SAD cohort. Criteria to stop dose escalation were met in the SAD 75-mg dose cohort, and remaining patients in this cohort received 50 mg. Subsequently, the final SAD cohort was completed using 40 mg of aficamten. CYP2D6-PM = cytochrome P450 2D6 poor metabolizer phenotype; d = day; LVEF = left ventricular ejection fraction; MAD = multiple-ascending dose; qd = once daily; SAD = single-ascending dose.

[0044] FIG. 3A shows mean (SE) maximum plasma concentration (C_{max}) of aficamten increased in a dose-proportional manner following single oral doses between 1 mg and 50 mg. FIG. 3B shows exposure (AUC_{24}) (B) of aficamten increased in a dose-proportional manner following single oral doses between 1 mg and 50 mg. AUC_{24} = area under the plasma drug concentration–time curve from 0 to 24 h; C_{max} = maximum plasma concentration; SE = standard error.

[0045] FIG. 4 shows plasma concentration over time with multiple doses of aficamten according to an exemplary clinical trial. Mean (SE) aficamten plasma concentrations are displayed. Data points are offset for clarity. Aficamten plasma concentrations increased between the 5-mg dose and the 2 higher doses; however, by day 2 there was no difference between mean concentrations of the 7.5-mg and 10-mg doses. Clearance was similar for the 5-mg and 10-mg doses, and the accumulation ratio was similar for all 3 doses. For days 7, 8, 10, 11, 12, and 13, only trough measurements are shown. For the 5-mg and 10-mg cohorts, the dosing period was 14 days with a 3-day follow-up. For the 7.5-mg cohort, dosing was