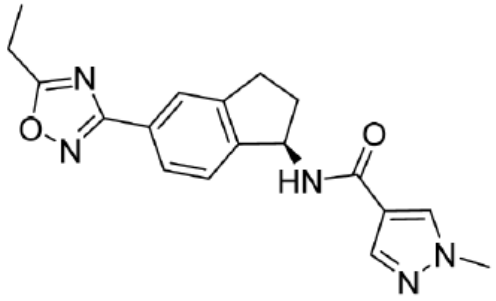
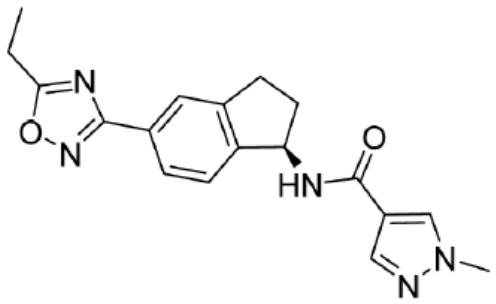
aficamten), or a pharmaceutically acceptable salt thereof, can be used to treat non-obstructive hypertrophic cardiomyopathy or hypertrophic cardiomyopathy with mid-ventricular obstruction. As further described herein, the daily dose of CK-274 may be titrated based on the results of an echocardiogram.

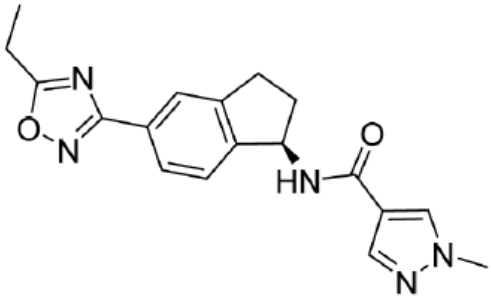
[0005] A method of treating non-obstructive hypertrophic cardiomyopathy (nHCM) or HCM with mid-ventricular obstruction (MVO, also known as "mid-cavitary obstruction") in a patient in need thereof can include administering to the patient a therapeutically effective amount of CK-274, or a pharmaceutically acceptable salt thereof, wherein the therapeutically effective amount of CK-274, or a pharmaceutically acceptable salt thereof, is selected by titrating a daily dose of CK-274, or a pharmaceutically acceptable salt thereof, administered to the patient. In one aspect, the present disclosure refers to use of CK-274



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-obstructive hypertrophic cardiomyopathy (nHCM) in a patient in need thereof, wherein a therapeutically effective amount of CK-274, or a pharmaceutically acceptable salt thereof, is selected by titrating a daily dose of CK-274, or a pharmaceutically acceptable salt thereof, to be administered to the patient. In another aspect, the present disclosure refers to use of CK-274



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-obstructive hypertrophic cardiomyopathy (nHCM) in a patient in need thereof. In yet another aspect, the present disclosure refers to use of CK-274



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating HCM with mid-ventricular obstruction (MVO) in a patient in need thereof, wherein a therapeutically effective amount of CK-274, or a pharmaceutically acceptable salt thereof, is selected by titrating a daily dose of CK-274, or a pharmaceutically acceptable salt thereof, to be 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.

[0006] In some examples of the above methods, CK-274, 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. 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 CK-274 free base or the corresponding amount of CK-274 free base when a non-free base form, e.g., a pharmaceutically acceptable salt, is administered.

[0007] 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.

[0008] In some examples, as described herein, a method, e.g., a method of treating non-obstructive hypertrophic cardiomyopathy (nHCM) or HCM with mid-ventricular obstruction (MVO) in a patient in need thereof, or a method for reducing angina frequency, in a patient in need thereof, comprises administering to the patient a first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a first time period, and a second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a second time period. In some examples, a first daily dose and a second daily dose are different. In some examples, a second daily dose is lower than the first daily dose. In some examples, a second daily dose is higher than the first daily dose. In some examples, a second daily dose is the same as the first daily dose. In some examples, a method further comprises administering

a third daily dose for a third time period as described herein. In some examples, a method further comprises administering a fourth daily dose for a fourth time period as described herein. Various technologies and criteria, e.g., biplane LVEF component of an echocardiogram after a daily dose for a time period, may be utilized to select a next daily dose. In some examples, a daily dose is of about 15 mg of CK-274 (e.g., as a third or a fourth daily dose).

[0009] In some examples, a method of treating non-obstructive hypertrophic cardiomyopathy (nHCM) or HCM with mid-ventricular obstruction (MVO) in a patient in need thereof comprises: administering to the patient a first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a first time period; and based on the biplane LVEF component of a first echocardiogram for the patient acquired after the first time period, administering to the patient a second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a second time period or terminating the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient. The method may include selecting the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, based on the biplane LVEF component of the first echocardiogram. 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.

[0010] In some examples of the above methods, the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient is terminated or interrupted 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%. For example, the predetermined biplane LVEF threshold may be 40%.

[0011] In some examples of the above methods, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is lower than the first daily dose of CK-274, 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%.

[0012] In some examples of the above methods, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is within the predetermined biplane LVEF thresholds. In some examples, the predetermined biplane LVEF thresholds are: biplane LVEF $\geq$ 50% and biplane LVEF $<$ 55%.

In some examples, the predetermined biplane LVEF thresholds are: biplane LVEF ≥ 50% and biplane LVEF < 60%.

[0013] In some examples of the above methods, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is at or above the predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 55%. In some examples, the predetermined biplane LVEF threshold is 60%.

[0014] In some examples of the above methods, the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg of CK-274. In some examples, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of CK-274.

[0015] 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.

[0016] In some examples of the above methods, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is administered to the patient for the second time period, and the method further comprises, based on the biplane LVEF of a second echocardiogram for the patient acquired after the second time period and the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, administering to the patient a third daily dose of CK-274, or a pharmaceutically acceptable salt thereof for a third time period or terminating the administering of CK-274, or a pharmaceutically acceptable salt thereof to the patient. In some examples, the method comprises selecting the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, based on the biplane LVEF of the second echocardiogram and the second daily dose. 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.

[0017] In some examples of the above methods, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is lower than the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, or the administering of CK-274, 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%.

[0018] In some examples of the above methods, the administering of CK-274, 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 CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof. In some examples, the predetermined biplane LVEF threshold is 50%. For example, if a method comprises treating the patient with a first daily dose of about 5 mg of CK-274 and a second daily dose of about 5 mg of CK-274, and if the biplane LVEF of the second echocardiogram is below the biplane LVEF threshold of 50%, then the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient is terminated.

[0019] In some examples of the above methods, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, when the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of CK-274, 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%. For example, if a method comprises treating the patient with a first daily dose of about 5 mg of CK-274 and a second daily dose of about 10 mg of CK-274, and if the biplane LVEF of the second echocardiogram is below the biplane LVEF threshold of 50%, then the third daily dose of CK-274 is returned to 5 mg of CK-274.

[0020] In some examples of the above methods, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the second echocardiogram is within the predetermined biplane LVEF thresholds. In some examples, the predetermined biplane LVEF thresholds are: biplane LVEF $\geq$ 50% and biplane LVEF $<$ 55%. In some examples, the predetermined biplane LVEF thresholds are: biplane LVEF $\geq$ 50% and biplane LVEF $<$ 60%.

[0021] In some examples of the above methods, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the second echocardiogram is at or above the predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 55%. In some examples, the predetermined biplane LVEF threshold is 60%.

[0022] In some examples of the above methods, the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg of CK-274, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of CK-274, and the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of CK-274.

[0023] In some examples of the above methods, the method further comprises measuring the component of the second echocardiogram.

[0024] In some examples of the above methods, the third time period is about 2 weeks.

[0025] In some examples of the above methods, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is administered to the patient for the third time period, the method further comprising, based on a component of a third echocardiogram for the patient acquired after the third time period and the third daily dose of Compound, or a pharmaceutically acceptable salt thereof, administering to the patient a fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a fourth time period or terminating the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient. In some examples, the method further comprises selecting the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, based on the biplane LVEF of the third echocardiogram and the third daily dose. 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.

[0026] In some examples of the above methods, the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is lower than the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, or the administering of CK-274, 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.

[0027] In some examples, the administering of CK-274, 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 CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, or lower. In some examples, the predetermined biplane LVEF threshold is 50%.

[0028] In some examples of the above methods, the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of CK-274, or a

pharmaceutically acceptable salt thereof, when the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is higher than the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the third echocardiogram is at or above the predetermined biplane LVEF threshold; or, the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, when the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the third echocardiogram is at or above the predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 50%.

[0029] In some examples of the above methods, the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the third echocardiogram is at or above the predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 55%. In some examples, the predetermined biplane LVEF threshold is 60%.

[0030] In some examples of the above methods, the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg of CK-274, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of CK-274, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of CK-274, and the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of CK-274.

[0031] In some examples, a daily dose is about 15 mg of CK-274. In some examples, a third daily dose is about 15 mg of CK-274. In some examples, a fourth daily dose is about 15 mg of CK-274. In some examples, a daily dose is about 20 mg of CK-274. In some examples, a fourth daily dose is about 20 mg of CK-274. In some examples, a daily dose is administered as a tablet. In some examples, amount of CK-274, 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 CK-274 in a tablet is about 5 mg. In some examples, the amount of CK-274 in a tablet is about 10 mg. In some examples, the amount of CK-274 in a tablet is about 15 mg. In some examples, the amount of CK-274 in a tablet is about 20 mg. In some examples, the amount of CK-274 in a tablet is about half of a daily dose

as described herein. In some examples, the amount of CK-274 in a tablet is about 2.5 mg. In some examples, the amount of CK-274 in a tablet is about 5 mg. In some examples, the amount of CK-274 in a tablet is about 7.5 mg. In some examples, the amount of CK-274 in a tablet is about 10 mg.

[0032] In some examples of the above methods, the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg of CK-274, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of CK-274, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of CK-274, and the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, about 15 mg, or about 20 mg of CK-274.

[0033] In some examples of the above methods, the method further comprises measuring the biplane LVEF of the third echocardiogram.

[0034] In some examples of the above methods, the fourth time period is about 2 weeks.

[0035] In some examples, a method of treating non-obstructive hypertrophic cardiomyopathy (nHCM) or HCM with mid-ventricular obstruction (MVO) in a patient in need thereof, comprises: administering to the patient a first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a first time period; and based a first echocardiogram comprising a biplane LVEF for the patient acquired after the first time period, administering to the patient a second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a second time period or terminating the administering of CK-274 to the patient, wherein: the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient is terminated if the biplane LVEF of the first echocardiogram is below a first predetermined biplane LVEF threshold; the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF is at or above the first predetermined biplane LVEF threshold and below a second predetermined biplane LVEF threshold; and the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF of the first echocardiogram is at or above the second predetermined biplane LVEF threshold.

[0036] In some examples of the above methods, the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg of CK-274 and the second daily dose

of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of CK-274.

[0037] In some examples of the above methods, the method further comprises measuring the biplane LVEF for the first echocardiogram.

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

[0039] In some examples of the above methods, the second time period is about 2 weeks.

[0040] In some examples of the above methods, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is administered to the patient for the second time period, the method further comprising, based a second echocardiogram comprising a biplane LVEF for the patient acquired after the second time period and the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, administering to the patient a third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a third time period or terminating the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient, wherein: the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient is terminated if the biplane LVEF of the second echocardiogram is below the first predetermined biplane LVEF threshold and the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof; the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is lower than the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF of the second echocardiogram is below the first predetermined biplane LVEF threshold and the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof; the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF is at or above the first predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; and the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF of the second echocardiogram is above the second predetermined biplane LVEF threshold.

[0041] In some examples of the above methods, the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg of CK-274, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of CK-

274, and the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of CK-274.

[0042] In some examples of the above methods, the method further comprises measuring the biplane LVEF for the second echocardiogram.

[0043] In some examples of the above methods, the third time period is about 2 weeks.

[0044] In some examples of the above methods, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is administered to the patient for the third time period, the method further comprising, based on a third echocardiogram comprising a biplane LVEF the patient acquired after the third time period and the third dose of CK-274, or a pharmaceutically acceptable salt thereof, administering to the patient a fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, for a fourth time period or terminating the administering of CK-274 to the patient, wherein: the administering of CK-274, or a pharmaceutically acceptable salt thereof, to the patient is terminated if the biplane LVEF of the third echocardiogram is below the first predetermined biplane LVEF threshold and the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof; the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is lower than the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF of the third echocardiogram is below the first predetermined biplane LVEF threshold and the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof; the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF is at or above the first predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; and the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, if the biplane LVEF of the third echocardiogram is at or above the second predetermined biplane LVEF threshold. In some examples, the first daily dose of CK-274, or a pharmaceutically acceptable salt thereof is about 5 mg of CK-274, the second daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of CK-274, the third daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of CK-274, and the fourth daily dose of CK-274, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, about 15 mg, or about 20 mg of CK-274. In some examples, the method further comprises measuring the

biplane LVEF for the third echocardiogram. In some examples, the third time period is about 2 weeks.

[0045] In some examples of the above methods, the first predetermined biplane LVEF threshold is 50%, and the second predetermined biplane LVEF threshold is 55%.

[0046] In some examples of the above methods, the first predetermined biplane LVEF threshold is 50%, and the second predetermined biplane LVEF threshold is 60%.

[0047] In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has end-diastolic left ventricular (LV) wall thickness ≥ 15 mm in one or more myocardial segments. In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has end-diastolic left ventricular (LV) wall thickness ≥ 13 mm in one or more wall segments and a known disease-causing gene mutation or positive family history of HCM.

[0048] In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has resting and post-Valsalva LVOT-G < 30 mmHg.

[0049] In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has resting LVOT-G < 30 mmHg. In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has a post-Valsalva LVOT-G < 50 mmHg. In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has resting LVOT-G < 30 mmHg and a post-Valsalva LVOT-G < 50 mmHg.

[0050] In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has KCCQ-CSS score of ≥ 30 and ≤ 85.

[0051] In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has elevated NT-proBNP. In some such examples, of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has NT-proBNP levels > 300 pg/mL. In some such examples, of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has NT-proBNP levels ≥ 900 pg/mL if in atrial fibrillation or atrial flutter. In some such examples, of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the

patient has an NT-pro BNP ≥ 225 pg/mL or NT-proBNP ≥ 675 pg/mL if in atrial fibrillation or atrial flutter.

[0052] In some examples of any of the above methods, prior to administration of CK-274, or a pharmaceutically acceptable salt thereof, the patient has left ventricular ejection fraction (LVEF) ≥60%.

[0053] In some examples of any of the above methods, the patient is not administered disopyramide during treatment with CK-274, or a pharmaceutically acceptable salt thereof.

[0054] In some examples of any of the above methods, the patient has not been treated with disopyramide or an antiarrhythmic drug that has negative inotropic activity within 4 weeks prior to treatment with CK-274, or a pharmaceutically acceptable salt thereof.

[0055] In some examples of any of the above methods, the patient is a CYP2D6 poor metabolizer.

[0056] In some examples of any of the above methods, the patient is fasting when administered CK-274, or a pharmaceutically acceptable salt thereof.

[0057] In some examples of any of the above methods, the patient is fed when administered CK-274, or a pharmaceutically acceptable salt thereof.

[0058] In some examples of any of the above methods, the method does not include taking a blood sample of the patient.

[0059] In some examples of any of the above methods, the method does not include analyzing a blood sample of the patient.

[0060] In some examples of any of the above methods, the patient is administered a beta-blocker during the treatment with CK-274, or a pharmaceutically acceptable salt thereof. In some examples of any of the above methods, the patient is administered one or more of a beta-blocker, verapamil, diltiazem, and ranolazine.

[0061] In some examples, the patient is obese. In some examples, the patient is not obese. In some examples, the patient has a body mass index (BMI) of 30 or greater. In some examples, the patient has a body mass index (BMI) of less than 30.

[0062] Also provided herein is a method of treating non-obstructive hypertrophic cardiomyopathy (nHCM) or HCM with mid-ventricular obstruction (MVO) in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of CK-274, or a pharmaceutically acceptable salt thereof.

[0063] In some examples of any of the above methods, the method results in one or more of the following: improvement in cardiac relaxation, beneficial cardiac remodeling, reverse cardiac remodeling, beneficial cardiac structural remodeling, beneficial cardiac functional

remodeling, reversal of adverse cardiac remodeling, reduction in mean left ventricular mass index (LVMI), improvement in left ventricular (LV) filling pressures, reduction in left atrial volume index (LAVI), reduction in the categorical assessment of systolic anterior motion of the mitral valve leaflet, reduction in systolic anterior motion of the mitral valve leaflet , reduction in the frequency of eccentric mitral regurgitation, reduction in mitral regurgitation, reduction in lateral E/e', reduction in lateral E/E, reduction in brain natriuretic peptide (BNP) and reduction in N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

[0064] In some examples, the one or more results of the treatment occur within 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of initiating treatment with CK-274, or a pharmaceutically acceptable salt thereof.

[0065] In some examples of any of the above methods, a left ventricle mass index (LVMI) for the patient is reduced.

[0066] In some examples of any of the above methods, a left arterial volume index (LAVI) for the patient is reduced.

[0067] In some examples of any of the above methods, an e' for the patient is reduced.

[0068] In some examples of any of the above methods, a lateral E/e' for the patient is reduced.

[0069] In some examples of any of the above methods, a likelihood systolic anterior motion of the mitral valve leaflet is reduced.

[0070] In some examples of any of the above methods, a level of brain natriuretic peptide or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the patient is decreased.

[0071] In some examples of any of the above methods, a level of cardiac troponin I in the patient is decreased.

[0072] In some examples of any of the above methods, left ventricular wall stress in the patient is decreased.

[0073] In some examples of any of the above methods, myocardial injury in the patient is decreased.

[0074] In some examples of any of the above methods, heart failure symptoms in the patient are reduced, for instance, the methods result in the reduction in the patient's NYHA classification.

[0075] In some examples of any of the above methods, the degree of mid-ventricular obstruction is reduced.

[0076] In some examples of any of the above methods, the method results in sustained effect(s) for at least 10 weeks, 12 weeks, 6 months, 1 year, 2 years, 3 years, 4 years, or 5 years.

[0077] In some examples of any of the above methods, administration for the second time period, third time period, or fourth time period may be, for example, administration for about 2 weeks, about 10 weeks, about 12 weeks, about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, or about 5 years, or indefinite. As used herein, administration for an indefinite time period may indicate: administration until the patient is no longer in need of treatment; administration until there is no further effect of treatment; or administration until there is no further reason for treatment.

[0078] In some examples, the methods result in a reduction in the patient's NYHA classification by one or more classes, and/or a decrease in NT-proBNP, and/or a decrease in the level of troponin I (e.g., cardiac troponin I).

[0079] In some examples of any of the above methods, the CK-274 or pharmaceutically acceptable salt thereof is administered orally. In some examples, the CK-274 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 CK-274 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 CK-274 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 CK-274.

BRIEF DESCRIPTION OF THE DRAWINGS

[0080] FIG. 1 illustrates and exemplary method for treating non-obstructive hypertrophic cardiomyopathy (nHCM) or HCM with mid-ventricular obstruction (MVO) in a patient that includes titrating the daily dose of CK-274, or a pharmaceutically acceptable salt thereof.