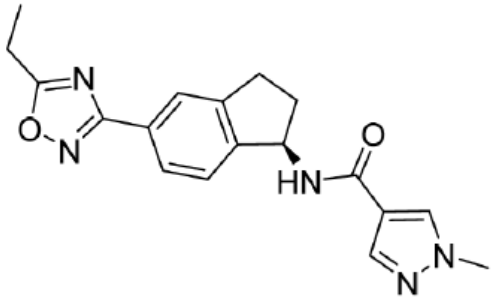
gradient (LVOT-G) to less than 50 mmHg in a patient with obstructive hypertrophic cardiomyopathy (oHCM). As further, described herein, the daily dose of Compound 1 may be titrated based on the results of an echocardiogram.

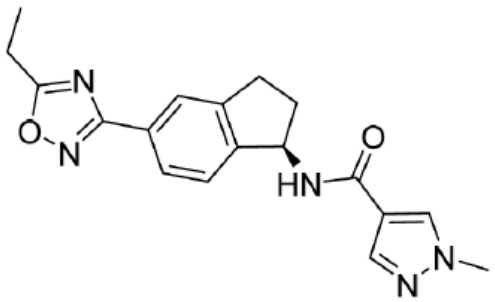
[0004a] In an aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for (a) reducing resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg, or (b) reducing post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, or (c) reducing resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg and reducing post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, in a patient with obstructive hypertrophic cardiomyopathy (oHCM).

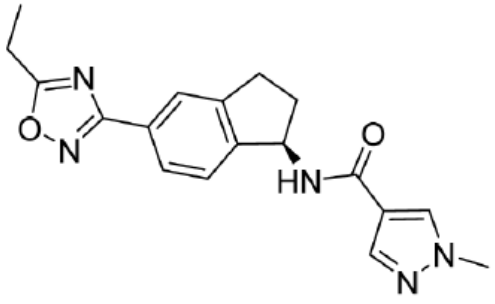
[0004b] In another aspect of the present disclosure, there is provided a use of a Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein said patient has a resting left ventricular outflow tract pressure gradient (LVOT-G) of at least 50 mmHg before Compound 1 or the pharmaceutically acceptable salt thereof is to be administered.

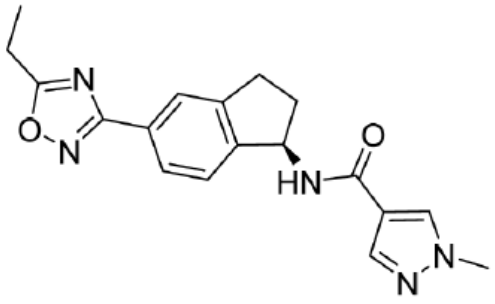
[0004c] In a further aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein said patient has a resting left ventricular outflow tract pressure gradient (LVOT-G) of at least 30 mmHg and less than 50 mmHg, and a post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) of at least 50 mmHg Compound 1 or the pharmaceutically acceptable salt thereof is to be administered.

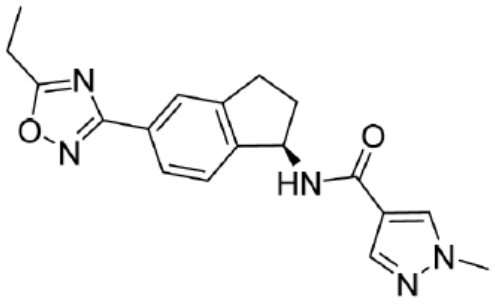
[0004d] In another aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein said patient is eligible for septal reduction therapy (SRT).

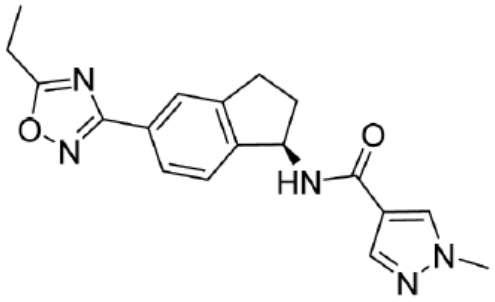
[0004e] In a further aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient with heart failure symptoms, wherein the use results in a reduction of heart failure symptoms as assessed by NYHA classification.

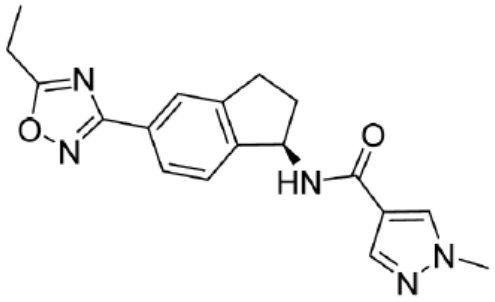
[0004f] In another aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing NT-proBNP levels in a patient.

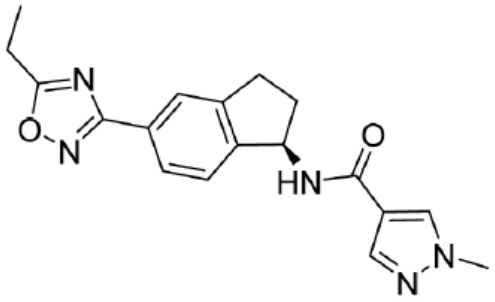
[0004g] In a further aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing cardiac troponin I levels in a patient.

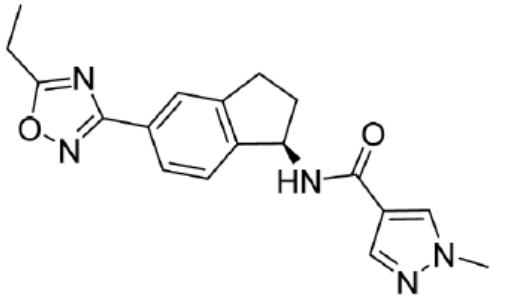
[0004h] In another aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for decreasing left ventricular wall stress in a patient, wherein the patient has obstructive hypertrophic cardiomyopathy (oHCM).

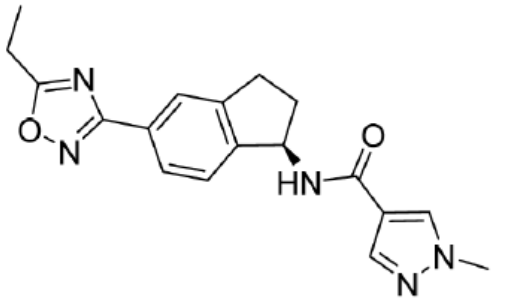
[0004i] In a further aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein a therapeutically effective amount of Compound 1 is to be administered to the patient, and wherein the therapeutically effective amount is selected by titrating a daily dose of Compound 1, or a pharmaceutically acceptable salt thereof.

[0004j] In another aspect of the present disclosure, there is provided a use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof,
wherein a first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered for a first time period, and

wherein based on one or more components of a first echocardiogram for the patient acquired after the first time period, a second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the patient for a second time period or the administration of Compound 1, or a pharmaceutically acceptable salt thereof, to the patient is terminated.

[0005] In an example, a method of reducing resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg in a patient with obstructive hypertrophic cardiomyopathy (oHCM) includes administering to the patient a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof. The reduction in resting LVOT-G to less than 30 mmHg may occur within ten weeks of initiating treatment with Compound 1, or a pharmaceutically acceptable salt thereof. The reduction in resting

LVOT-G to less than 30 mmHg may occur within two weeks of initiating treatment with Compound 1, or a pharmaceutically acceptable salt thereof. In some implementations, reduction in resting LVOT-G is sustained for at least 10 weeks of treatment. In some examples, the reduction in resting LVOT-G occurs within two to six weeks of the end of a dose titration. In some examples, the reduction in resting LVOT-G peaks within two to six weeks of the end of a dose titration.

[0006] In some implementations, a method of reducing post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg in a patient with obstructive hypertrophic cardiomyopathy (oHCM) includes administering to the patient a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof. The reduction in post-Valsalva LVOT-G to less than 50 mmHg may occur within two weeks of initiating treatment with Compound 1, or a pharmaceutically acceptable salt thereof. The reduction in post-Valsalva LVOT-G may be sustained for at least 10 weeks of treatment. In some examples, the reduction in post-Valsalva LVOT-G occurs within two to six weeks of the end of dose titration. In some examples, the reduction in post-Valsalva LVOT-G peaks within two to six weeks of the end of dose titration.

[0007] 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 Compound 1, or a pharmaceutically acceptable salt thereof, wherein the therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, is selected by titrating a daily dose of Compound 1, 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.

[0008] In some implementations of the above methods, Compound 1, or a pharmaceutically acceptable salt thereof is administered at a daily dose of about 5 mg to about 30 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. In some examples, the daily dose is about 30 mg.

[0009] In some implementations, the daily dose is administered as a single dose each day. In some implementations, the daily dose is administered in 2 divided doses.

[0010] 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 Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, for a second time period or terminating the administering of Compound 1, or a pharmaceutically acceptable salt thereof, to the patient. The method may include selecting the second daily dose of Compound 1, 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, a post-Valsalva LVOT-G, or a resting LVOT-G. In some examples, the one or more components of the first echocardiogram comprises a biplane LVEF, a post-Valsalva LVOT-G, and a resting LVOT-G. In some examples, the one or more components of the first echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G.

[0011] In some implementations of the above method, the one or more components of the first echocardiogram comprises a biplane LVEF, and the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is lower than the first daily dose of Compound 1, 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 implementations of the above method, the one or more components of the first echocardiogram comprises a biplane LVEF, and the administering of Compound 1, 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%.

[0013]In some implementations of the above method, the one or more components of the first echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is at or above the predetermined biplane LVEF threshold, the resting LVOT-G of the first echocardiogram is below a predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G of the first echocardiogram is below a predetermined post-Valsalva LVOT-G threshold. In some examples, the predetermined biplane LVEF threshold is 50%, the predetermined resting LVOT-G threshold is 30 mmHg, and the post-Valsalva LVOT-G threshold is 50 mmHg.

[0014]In some implementations of the above method, the one or more components of the first echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the first echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and the resting LVOT-G is at or above the predetermined resting LVOT-G threshold, or (2) the biplane LVEF is at or above the predetermined biplane LVEF threshold, the resting LVOT-G is below the predetermined resting LVOT-G 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 50%, the predetermined resting LVOT-G threshold is 30 mmHg, and the post-Valsalva LVOT-G threshold is 50 mmHg.

[0015]In some implementations 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the first echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and below a second predetermined biplane LVEF threshold; or (2) the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G of the first echocardiogram is below a second predetermined post-Valsalva LVOT-G 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.

[0016] In some implementations 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 Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of Compound 1 when the biplane LVEF of the first echocardiogram is above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G of the first echocardiogram is at or above the second predetermined post-Valsalva LVOT-G 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.

[0017] In some implementations of the above method, the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1. In some examples, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1.

[0018] In some implementations of the above method, the method further comprises measuring the one or more components of the first echocardiogram.

[0019] In some implementations of the above method, first time period is about 2 weeks. In some examples, the second time period is about 2 weeks.

[0020] In some implementations of the above method, the second daily dose of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, administering to the patient a third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof for a third time period or terminating the administering of Compound 1, or a pharmaceutically acceptable salt thereof to the patient. In some examples, the method comprises selecting the third daily dose of Compound 1, 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, a post-Valsalva LVOT-G, or a resting LVOT-G. In some examples, the one or more components of the second echocardiogram comprises a biplane LVEF, a post-Valsalva LVOT-G, and a resting LVOT-G. In some examples, the one or more

components of the second echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G.

[0021] In some examples of the above method, the one or more components of the second echocardiogram comprises a biplane LVEF, and the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is lower than the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, or the administering of Compound 1, 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%.

[0022] In some examples of the above method, the administering of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof is the same as the first daily dose of Compound 1 or lower. In some examples, the predetermined biplane LVEF threshold is 50%.

[0023] In some examples of the above method, the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of Compound 1, 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%.

[0024] In some examples of the above method, the one or more components of the second echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof when the biplane LVEF of the second echocardiogram is at or above the predetermined biplane LVEF threshold, the resting LVEOT-G of the second echocardiogram is below the predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G of the second echocardiogram is below the predetermined post-Valsalva LVOT-G threshold. In some examples, the predetermined biplane LVEF threshold is 50%, the predetermined resting LVOT-G threshold is 30 mmHg, and the post-Valsalva LVOT-G threshold is 50 mmHg.

[0025] In some examples of the above method, the one or more components of the second echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the second echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and the resting LVEOT-G is at or above the predetermined resting LVOT-G threshold, or (2) the biplane LVEF is at or above the predetermined biplane LVEF threshold, the resting LVOT-G is below the predetermined resting LVOT-G 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 50%, the predetermined resting LVOT-G threshold is 30 mmHg, and the post-Valsalva LVOT-G threshold is 50 mmHg.

[0026] In some examples of the above method, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the second echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; or (2) the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is below the second predetermined post-Valsalva LVOT-G 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.

[0027] In some examples of the above method, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of Compound 1, 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 second predetermined post-Valsalva LVOT-G 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.

[0028] In some examples of the above method, the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1, and the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of Compound 1.

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

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

[0031] In some examples of the above method, the third daily dose of Compound 1, 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 Compound, or a pharmaceutically acceptable salt thereof, administering to the patient a fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, for a fourth time period or terminating the administering of Compound 1, or a pharmaceutically acceptable salt thereof, to the patient. In some examples, the method further comprises selecting the fourth daily dose of Compound 1, 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, a post-Valsalva LVOT-G, or a resting LVOT-G. In some examples, the one or more components of the third echocardiogram comprises a biplane LVEF, a post-Valsalva LVOT-G, and a resting LVOT-G. In some examples, the one or more components of the third echocardiogram comprises a biplane LVEF and a post-Valsalva LVOT-G.

[0032] In some examples of the above method, the one or more components of the third echocardiogram comprises a biplane LVEF, and the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is lower than the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, or the administering of Compound 1, 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 Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, or lower. In some examples, the predetermined biplane LVEF threshold is 50%.

[0033] In some examples of the above method, the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is higher than the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the third echocardiogram is below the predetermined biplane LVEF threshold; or the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the third echocardiogram is below the predetermined biplane LVEF threshold. In some examples, the predetermined biplane LVEF threshold is 50%.

[0034] In some examples of the above method, the one or more components of the third echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the third echocardiogram is at or above the predetermined biplane LVEF threshold, the resting LVEOT-G of the third echocardiogram is below the predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G of the third echocardiogram is below the predetermined post-Valsalva LVOT-G threshold. In some examples, the predetermined biplane LVEF threshold is 50%, the predetermined resting LVOT-G threshold is 30 mmHg, and the post-Valsalva LVOT-G threshold is 50 mmHg.

[0035] In some examples of the above method, the one or more components of the third echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the third echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and the resting LVEOT-G is at or above the predetermined resting LVOT-G threshold, or (2) the biplane LVEF is at or above the predetermined biplane LVEF threshold, the resting LVOT-G is

below the predetermined resting LVOT-G 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 50%, the predetermined resting LVOT-G threshold is 30 mmHg, and the post-Valsalva LVOT-G threshold is 50 mmHg.

[0036] In some examples of the above method, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the third echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; or (2) the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is below the second predetermined post-Valsalva LVOT-G 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.

[0037] In some examples of the above method, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of Compound 1, 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 second predetermined post-Valsalva LVOT-G 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.

[0038] In some examples of the above method, the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1, the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of Compound 1, and the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, about 15 mg, or about 20 mg of Compound 1.

[0039] In some examples of the above method, the method further comprises measuring the one or more components of the third echocardiogram.

[0040] In some examples of the above method, the fourth time period is about 2 weeks.

[0041] In some implementation, a method of treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, comprises: administering to the patient a first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, for a first time period; and based on a first echocardiogram comprising a biplane LVEF and a post-Valsalva LVOT-G for the patient acquired after the first time period, administering to the patient a second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, for a second time period or terminating the administering of Compound 1 to the patient, wherein: the administering of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, if either of the following conditions are met on the first echocardiogram: (1) the biplane LVEF is at or above the first predetermined biplane LVEF threshold and below a second predetermined biplane LVEF threshold; or (2) the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is below a predetermined post-Valsalva LVOT-G threshold; and the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, if the biplane LVEF of the first echocardiogram is above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G of the first echocardiogram is at or above the predetermined post-Valsalva LVOT-G threshold.

[0042] In some examples of the above method, the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1 and the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1.

[0043] In some examples of the above method, the method further comprises measuring the biplane LVEF and the post-Valsalva LVOT-G for the first echocardiogram.

[0044] In some examples of the above method, the first time period is about 2 weeks.

[0045] In some examples of the above method, the second time period is about 2 weeks.

[0046] In some examples of the above method, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is administered to the patient for the second time period, the method further comprising, based on a second echocardiogram comprising a biplane LVEF and a post-Valsalva LVOT-G for the patient acquired after the second time

period and the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, administering to the patient a third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, for a third time period or terminating the administering of Compound 1, or a pharmaceutically acceptable salt thereof, to the patient, wherein: the administering of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof; the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is lower than the second daily dose of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof; the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, if either of the following conditions are met on the second echocardiogram: (1) the biplane LVEF is at or above the first predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; or (2) 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; and the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, if 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.

[0047] In some examples of the above method, the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1, and the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of Compound 1.

[0048] In some examples of the above method, the method further comprises measuring the biplane LVEF and the post-Valsalva LVOT-G for the second echocardiogram.

[0049] In some examples of the above method, the third time period is about 2 weeks.

[0050] In some examples of the above method, the third daily dose of Compound 1, 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 and a post-Valsalva LVOT-G for the patient acquired after the third time period and the second third dose of Compound 1, or a pharmaceutically acceptable salt thereof, administering to the patient a fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, for a fourth time period or terminating the administering of Compound 1 to the patient, wherein: the administering of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof; the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is lower than the third daily dose of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof; the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, if either of the following conditions are met on the third echocardiogram: (1) the biplane LVEF is at or above the first predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; or (2) 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; and the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, if 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 first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof is about 5 mg of Compound 1, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1, the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of Compound 1, and the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, about 15 mg, or about

20 mg of Compound 1. In some examples, the method further comprises measuring the biplane LVEF and the post-Valsalva LVOT-G for the second echocardiogram. In some examples, the third time period is about 2 weeks.

[0051] In some examples of the above method, 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.

[0052] In some examples of any of the above methods, prior to administration of Compound 1, or a pharmaceutically acceptable salt thereof, the patient has (i) resting LVOT-G ≥50 mmHg; or (ii) resting LVOT-G ≥30 mmHg and <50 mmHg with post-Valsalva LVOT-G ≥50 mmHg.

[0053] In some examples of any of the above methods, prior to administration of Compound 1, or a pharmaceutically acceptable salt thereof, the patient has left ventricular ejection fraction (LVEF) ≥60%.

[0054] In some examples of any of the above methods, the patient is not administered disopyramide during treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

[0055] In some examples of any of the above methods, the patient is administered disopyramide during the treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

[0056] 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 Compound 1, or a pharmaceutically acceptable salt thereof.

[0057] In some examples of any of the above methods, the patient is administered an antiarrhythmic medication during the treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

[0058] In some examples of any of the above methods, the patient is a CYP2D6 poor metabolizer.

[0059] In some examples of any of the above methods, the patient is fasting when administered Compound 1, or a pharmaceutically acceptable salt thereof.

[0060] In some examples of any of the above methods, the patient is fed when administered Compound 1, or a pharmaceutically acceptable salt thereof.

[0061] In some examples of any of the above methods, the method does not include taking a blood sample of the patient.

[0062] In some examples of any of the above methods, the method does not include analyzing a blood sample of the patient.

[0063] In some examples of any of the above methods, the patient is administered a beta-blocker during the treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

[0064] Also provided herein is a method of treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0065] In some examples of any of the above methods, the method results in one or more of the following: improvement in mitral regurgitation, 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).

[0066] 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 Compound 1, or a pharmaceutically acceptable salt thereof.

[0067] In some examples of any of the above methods, a left ventricle mass index (LVMI) for the patient is reduced.

[0068] In some examples of any of the above methods, a left arterial volume index (LAVI) for the patient is reduced.

[0069] In some examples of any of the above methods, an e' for the patient is reduced.

[0070] In some examples of any of the above methods, a lateral E/e' for the patient is reduced.

[0071] In some examples of any of the above methods, a likelihood systolic anterior motion of the mitral valve leaflet is reduced.

[0072] In some examples of any of the above methods, a likelihood of mitral regurgitation is reduced.

[0073] 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.

[0074] In some examples of any of the above methods, a level of cardiac troponin I in the patient is decreased.

[0075] In some examples of any of the above methods, left ventricular wall stress in the patient is decreased.

[0076] In some examples of any of the above methods, myocardial injury in the patient is decreased.

[0077] 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.

[0078] 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.

[0079] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

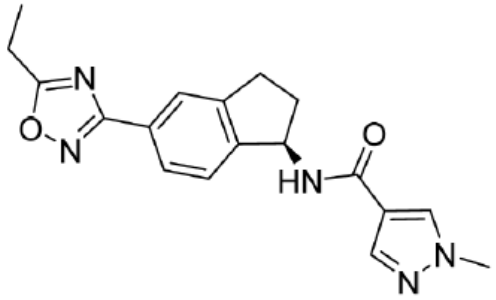
[0080] FIG. 1 illustrates and exemplary method for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient that included titrating the daily dose of CK-274, or a pharmaceutically acceptable salt thereof.

[0081] FIG. 2 shows a schematic overview of a phase 1 clinical study for CK-274 (also referred to as 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

CLAIMS

What is claimed is:

1. Use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for (a) reducing resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg, or (b) reducing post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, or (c) reducing resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg and reducing post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, in a patient with obstructive hypertrophic cardiomyopathy (oHCM).

2. The use of claim 1, wherein the reduction in resting LVOT-G to less than 30 mmHg, reduction in post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, or reduction in resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg and reduction in post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg occurs within ten weeks of initiating treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

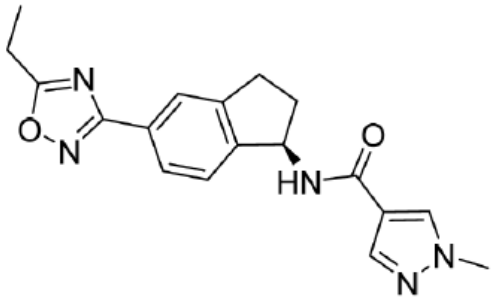
3. The use of claim 2, wherein the reduction in resting LVOT-G to less than 30 mmHg, reduction in post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, or reduction in resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg and reduction in post-Valsalva left ventricular outflow tract pressure gradient

(LVOT-G) to less than 50 mmHg occurs within two weeks of initiating treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1-3, wherein the reduction in resting LVOT-G to less than 30 mmHg, reduction in post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, or reduction in resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg and reduction in post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg is sustained for at least 10 weeks of treatment.

5. The use of any one of claims 1-4, wherein the reduction in resting LVOT-G to less than 30 mmHg, reduction in post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg, or reduction in resting left ventricular outflow tract pressure gradient (LVOT-G) to less than 30 mmHg and reduction in post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) to less than 50 mmHg peaks within two to six weeks of the end of a dose titration.

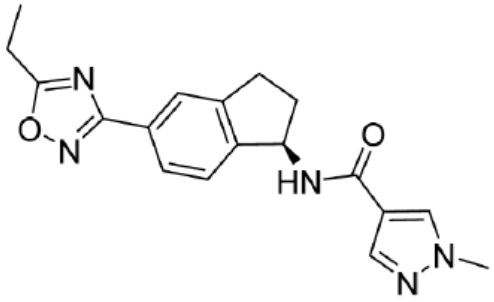
6. Use of a Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein said patient has a resting left ventricular outflow tract pressure gradient (LVOT-G) of at least 50 mmHg before Compound 1 or the pharmaceutically acceptable salt thereof is to be administered.

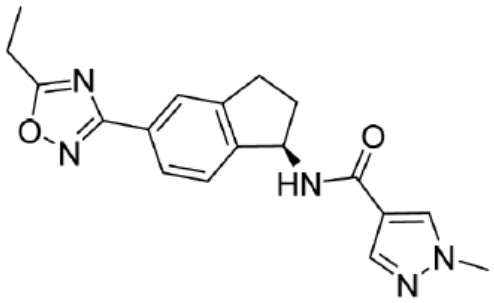
7. Use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein said patient has a resting left ventricular outflow tract pressure gradient (LVOT-G) of at least 30 mmHg and less than 50 mmHg, and a post-Valsalva left ventricular outflow tract pressure gradient (LVOT-G) of at least 50 mmHg Compound 1 or the pharmaceutically acceptable salt thereof is to be administered.

8. Use of Compound 1,



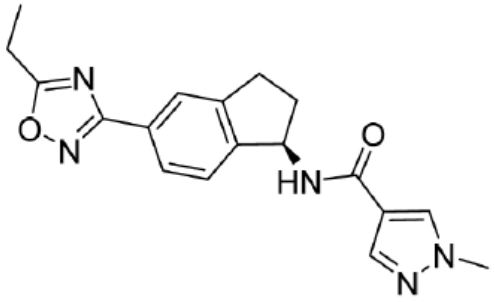
(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein said patient is eligible for septal reduction therapy (SRT).

9. The use of claim 8, wherein the use precludes the need of septal reduction therapy in the patient.

10. The use of claim 8 or 9, wherein the septal reduction therapy is myectomy or alcohol septal ablation.

11. Use of Compound 1,



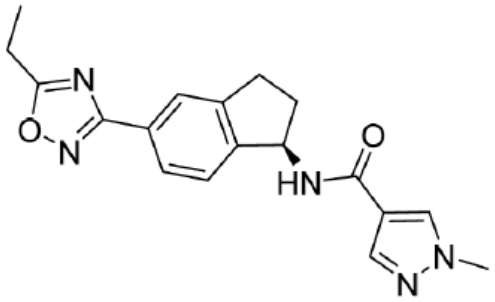
(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient with heart failure symptoms, wherein the use results in a reduction of heart failure symptoms as assessed by NYHA classification.

12. The use of claim 11, wherein the use results in improvement by one NYHA class or two NYHA classes in the patient.

13. The use of claim 11 or 12, wherein the reduction of heart failure symptoms occurs within ten weeks of initiating treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

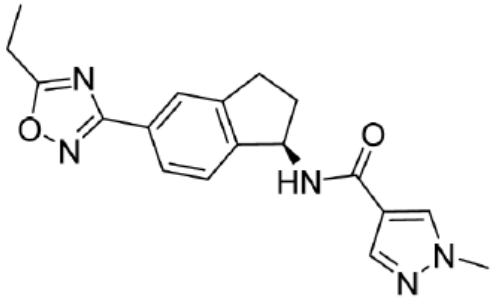
14. Use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing NT-proBNP levels in a patient.

15. Use of Compound 1,



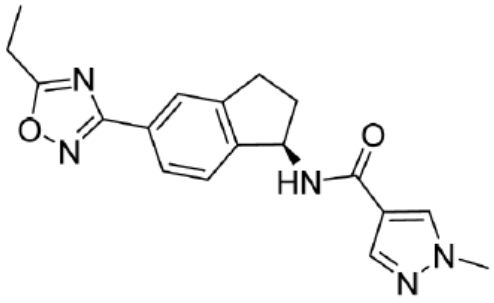
(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing cardiac troponin I levels in a patient.

16. The use of claim 14 or 15, wherein the patient has obstructive hypertrophic cardiomyopathy (oHCM).

17. The use of any one of claims 1-16, wherein the use decreases left ventricular wall stress in the patient.

18. Use of Compound 1,

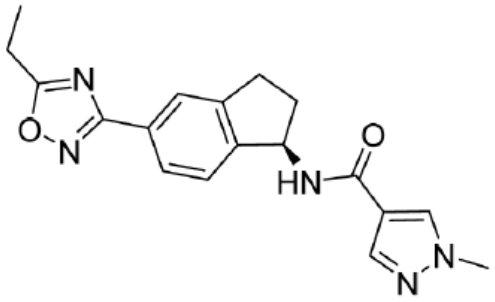


(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for decreasing left ventricular wall stress in a patient, wherein the patient has obstructive hypertrophic cardiomyopathy (oHCM).

19. The use of any one of claims 1-18, wherein a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the patient, and wherein the therapeutically effective amount is selected by titrating a daily dose of Compound 1, or the pharmaceutically acceptable salt thereof.

20. Use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof, wherein a therapeutically effective amount of Compound 1 is to be administered to the patient, and wherein the therapeutically effective amount is selected by titrating a daily dose of Compound 1, or a pharmaceutically acceptable salt thereof.

21. The use of claim 19 or 20, wherein the dose is titrated once during a course of treatment.

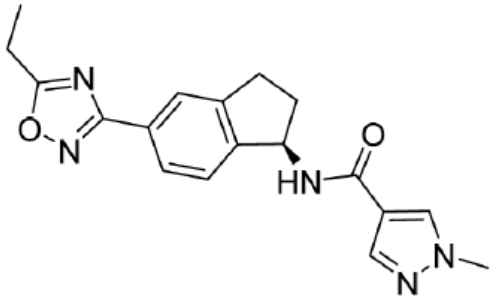
22. The use of claim 19 or 20, wherein the dose is titrated two or more times during a course of treatment.

23. The use of any one of claims 19-22, wherein a daily dose is to be administered to a patient at a constant amount for about two weeks before the daily dose amount is titrated.

24. The use of any one of claims 1-23, wherein a daily dose of about 5 mg to about 30 mg of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered.

25. The use of claim 24, wherein the daily dose is about 5 mg, about 10 mg, about 15 mg, about 20 mg, or about 30 mg.

26. Use of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating obstructive hypertrophic cardiomyopathy (oHCM) in a patient in need thereof,

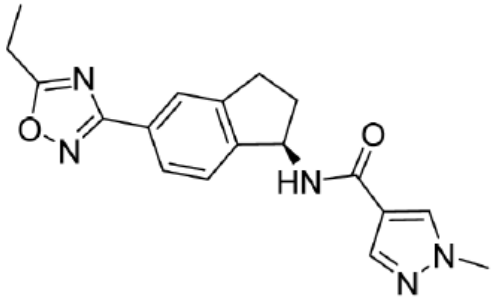
wherein a first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered for a first time period, and

wherein based on one or more components of a first echocardiogram for the patient acquired after the first time period, a second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the patient for a second time period or the administration of Compound 1, or a pharmaceutically acceptable salt thereof, to the patient is terminated.

27. The use of claim 26, wherein the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is selected based on the one or more components of the first echocardiogram.

28. The use of claim 26 or 27, wherein the one or more components of the first echocardiogram comprises (a) a biplane LVEF, (b) a post-Valsalva LVOT-G, (c) a resting LVOT-G, (d) a biplane LVEF and a post-Valsalva LVOT-G, or (e) a biplane LVEF, a post-Valsalva LVOT-G, and a resting LVOT-G.

29. The use of any one of claims 26-28, wherein the one or more components of the first echocardiogram comprises a biplane LVEF, and the second daily dose of Compound 1,



(Compound 1),

or a pharmaceutically acceptable salt thereof, is lower than the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is below a predetermined biplane LVEF threshold.

30. The use of any one of claims 26-28, wherein the one or more components of the first echocardiogram comprises a biplane LVEF, and the administration of Compound 1, 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.

31. The use of any one of claims 26-28, wherein the one or more components of the first echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the first echocardiogram is at or above the predetermined biplane LVEF threshold, the resting LVOT-G of the first echocardiogram is below a predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G of the first echocardiogram is below a predetermined post-Valsalva LVOT-G threshold.

32. The use of any one of claims 26-28, wherein the one or more components of the first echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the first echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and the resting LVOT-G is at or above the predetermined resting LVOT-G threshold, or (2) the biplane LVEF is at or above the

predetermined biplane LVEF threshold, the resting LVOT-G is below the predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G is at or above the predetermined post-Valsalva LVOT-G threshold.

33. The use of any one of claims 26-28, wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the first echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and below a second predetermined biplane LVEF threshold; or (2) the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G of the first echocardiogram is below a second predetermined post-Valsalva LVOT-G threshold.

34. The use of any one of claims 26-28, wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the first daily dose of Compound 1 when the biplane LVEF of the first echocardiogram is above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G of the first echocardiogram is at or above the second predetermined post-Valsalva LVOT-G threshold.

35. The use of any one of claims 26-34, wherein the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1.

36. The use of claim 35, wherein the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1.

37. The use of any one of claims 26-36, further comprising measuring the one or more components of the first echocardiogram.

38. The use of any one of claims 26-37, wherein the first time period is about 2 weeks.

39. The use of any one of claims 26-38, wherein the second time period is about 2 weeks.

40. The use of any one of claims 26-39, wherein the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the patient for the second time period, and wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof, a third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof is to be administered to the patient for a third time period or the administration of Compound 1, or a pharmaceutically acceptable salt thereof to the patient is terminated.

41. The use of claim 40, comprising selecting the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, based on the one or more components of the second echocardiogram and the second daily dose.

42. The use of claim 40 or 41, wherein the one or more components of the second echocardiogram comprises (a) a biplane LVEF, (b) a post-Valsalva LVOT-G, (c) a resting LVOT-G, (d) a biplane LVEF and a post-Valsalva LVOT-G, or (e) a biplane LVEF, a post-Valsalva LVOT-G, and a resting LVOT-G.

43. The use of any one of claims 40-42, wherein the one or more components of the second echocardiogram comprises a biplane LVEF, and the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is lower than the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, or the administration of Compound 1, 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.

44. The use of any one of claims 40-42, wherein the administration of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof is the same as the first daily dose of Compound 1 or lower.

45. The use of any one of claims 40-42, wherein the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is higher than the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the second echocardiogram is below the predetermined biplane LVEF threshold.

46. The use of any one of claims 40-42, wherein the one or more components of the second echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof when the biplane LVEF of the second echocardiogram is at or above the predetermined biplane LVEF threshold, the resting LVEOT-G of the second echocardiogram is below the predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G of the second echocardiogram is below the predetermined post-Valsalva LVOT-G threshold.

47. The use of any one of claims 40-42, wherein the one or more components of the second echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the second echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and the resting LVEOT-G is at or above the predetermined resting LVOT-G threshold, or (2) the biplane LVEF is at or above the predetermined biplane LVEF threshold, the resting LVOT-G is below the predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G is at or above the predetermined post-Valsalva LVOT-G threshold.

48. The use of any one of claims 40-42, wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the second echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; or (2) the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is below the second predetermined post-Valsalva LVOT-G threshold.

49. The use of any one of claims 40-42, wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the second daily dose of Compound 1, 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 second predetermined post-Valsalva LVOT-G threshold.

50. The use of any one of claims 40-49, wherein the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1, and the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of Compound 1.

51. The use of any one of claims 40-50, further comprising measuring the one or more components of the second echocardiogram.

52. The use of any one of claims 40-51, wherein the third time period is about 2 weeks.

53. The use of any one of claims 40-52, wherein the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the patient for the third time

period, and wherein 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 Compound, or a pharmaceutically acceptable salt thereof, a fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the patient for a fourth time period or the administration of Compound 1, or a pharmaceutically acceptable salt thereof, to the patient is terminated.

54. The use of claim 53, comprising selecting the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, based on the one or more components of the third echocardiogram and the third daily dose.

55. The use of claim 53 or 54, wherein the one or more components of the third echocardiogram comprises (a) a biplane LVEF, (b) a post-Valsalva LVOT-G, (c) a resting LVOT-G, (d) a biplane LVEF and a post-Valsalva LVOT-G, or (e) a biplane LVEF, a post-Valsalva LVOT-G, and a resting LVOT-G.

56. The use of any one of claims 53-55, wherein the one or more components of the third echocardiogram comprises a biplane LVEF, and the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is lower than the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, or the administration of Compound 1, 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.

57. The use of any one of claims 53-55, wherein the administration of Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, or lower.

58. The use of any one of claims 53-55, wherein:

the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof,

when the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is higher than the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the third echocardiogram is below the predetermined biplane LVEF threshold; or

the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, and the biplane LVEF of the third echocardiogram is below the predetermined biplane LVEF threshold.

59. The use of any one of claims 53-55, wherein the one or more components of the third echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when the biplane LVEF of the third echocardiogram is at or above the predetermined biplane LVEF threshold, the resting LVOT-G of the third echocardiogram is below the predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G of the third echocardiogram is below the predetermined post-Valsalva LVOT-G threshold.

60. The use of any one of claims 53-55, wherein the one or more components of the third echocardiogram comprises a biplane LVEF, a resting LVOT-G, and a post-Valsalva LVOT-G, and wherein the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the third echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and the resting LVOT-G is at or above the predetermined resting LVOT-G threshold, or (2) the biplane LVEF is at or above the predetermined biplane LVEF threshold, the resting LVOT-G is below the predetermined resting LVOT-G threshold, and the post-Valsalva LVOT-G is at or above the predetermined post-Valsalva LVOT-G threshold.

61. The use of any one of claims 53-55, wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof, is the same as the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, when either of the following conditions are met on the third echocardiogram: (1) the biplane LVEF is at or above the predetermined biplane LVEF threshold and below the second predetermined biplane LVEF threshold; or (2) the biplane LVEF is at or above the second predetermined biplane LVEF threshold and the post-Valsalva LVOT-G is below the second predetermined post-Valsalva LVOT-G threshold.

62. The use of any one of claims 53-55, wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof, is greater than the third daily dose of Compound 1, 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 second predetermined post-Valsalva LVOT-G threshold.

63. The use of any one of claims 53-62 wherein the first daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg of Compound 1, the second daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg or about 10 mg of Compound 1, the third daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, or about 15 mg of Compound 1, and the fourth daily dose of Compound 1, or a pharmaceutically acceptable salt thereof, is about 5 mg, about 10 mg, about 15 mg, or about 20 mg of Compound 1.

64. The use of any one of claims 53-63, wherein the one or more components of the third echocardiogram is further measured.

65. The use of any one of claims 53-64, wherein the fourth time period is about 2 weeks.

66. The use of any one of claims 29-65, wherein

(a) the predetermined biplane LVEF threshold is 50%;

(b) the predetermined biplane LVEF threshold is 50%, the predetermined resting LVOT-G threshold is 30 mmHg, and the predetermined post-Valsalva LVOT-G threshold is 50 mmHg; or

(c) 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.

67. The use of any one of claims 1-66, wherein the patient has (i) resting LVOT-G ≥50 mmHg; or (ii) resting LVOT-G ≥30 mmHg and <50 mmHg with post-Valsalva LVOT-G ≥50 mmHg before Compound 1, or a pharmaceutically acceptable salt thereof is to be administered.

68. The use of any one of claims 1-67, wherein the patient has left ventricular ejection fraction (LVEF) ≥60% before Compound 1, or a pharmaceutically acceptable salt thereof is to be administered.

69. The use of any one of claims 1-68, wherein the patient is not administered disopyramide during treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

70. The use of any one of claims 1-68, wherein the patient is to be administered disopyramide during the treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

71. The use of any one of claims 1-68, wherein the patient has not been treated with disopyramide or an antiarrhythmic drug that has negative inotropic activity within 4 weeks prior to treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

72. The use of any one of claims 1-68 or 70, wherein the patient is to be administered an antiarrhythmic medication during the treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

73. The use of any one of claims 1-72, wherein the patient is a CYP2D6 poor metabolizer.

74. The use of any one of claims 1-73, wherein the patient is fasting when Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered.

75. The use of any one of claims 1-73, wherein the patient is fed when Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered.

76. The use of any one of claims 1-75, wherein the use does not include taking a blood sample of the patient.

77. The use of any one of claims 1-76, wherein the use does not include analyzing a blood sample of the patient.

78. The use of any one of claims 1-77, wherein the patient is to be administered a beta-blocker during the treatment with Compound 1, or a pharmaceutically acceptable salt thereof.

79. The use of any one of claims 1-78, wherein the use results in one or more of the following: improvement in mitral regurgitation, 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).

80. The use of any one of claims 1-79, wherein the use results in one or more of the following: improvement in exercise capacity, improvement in peak oxygen uptake, improvement

in peak oxygen uptake (pVO2) by cardiopulmonary exercise testing (CPET), improvement in Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS), Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), improvement in quality of life, improvement in quality of life as measured by PRO questionnaire, improvement in NYHA Functional Classification by one or more class(es), improvement in post-Valsalva left ventricular outflow tract gradient (LVOT-G), and improvement in total workload during CPET.

81. The use of claim 80, wherein the use results in:

(a) change from baseline of ≥1.5 mL/kg/min in pVO2 and improvement in NYHA Functional Class by one or more class(es)

(b) change from baseline of ≥3.0 mL/kg/min in pVO2 and no worsening of NYHA Functional Class

82. The use of claim 80 or 81, wherein the use results in improvement in KCCQ-OSS or KCCQ-CSS by at least 5 points, at least 10 points, or at least 20 points .

83. The use of any one of claims 80-82, wherein the use results in resting LVOT-G <30 mmHg, post-Valsalva LVOT-G <50 mmHg, and improvement in NYHA Functional Class by one or more class(es).

84. The use of any one of claims 1-83, wherein the use decreases myocardial injury in the patient.

85. The use of any one of claims 1-84, wherein (a) the daily dose is to be administered as a single dose each day or (b) the daily dose is to be administered in 2 divided doses.

86. The use of any one of claims 1-85, wherein Compound 1, or a pharmaceutically acceptable salt thereof, has a sustained effect for at least 10 weeks, 12 weeks, 6 months, 1 year, 2 years, 3 years, 4 years, or 5 years.

87. The use of any one of claims 79-86, wherein 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 Compound 1, or a pharmaceutically acceptable salt thereof.