Claims

We claim:

1. Use of a myosin inhibitor in the manufacture of a medicament for the treatment of ~~A method of treating~~ a patient having cardiac hypercontractility, impaired cardiac relaxation and/or left ventricular hypertrophy, wherein the patient is undergoing β blocker therapy, ~~the method comprising:~~

wherein the patient is to be administered ~~administering to the patient~~ a therapeutically effective amount of a myosin inhibitor during a first treatment phase during which the patient also receives β blocker therapy; and

wherein the patient is to be administered ~~continuing to administer to the patient~~ a therapeutically effective amount of a myosin inhibitor during a second treatment phase during which the patient either (a) does not receive β blocker therapy, or (b) receives a reduced amount of β blocker therapy.

2. The ~~method~~ use of claim 1, wherein the patient does not receive β blocker therapy during the second treatment phase.

3. The ~~method~~ use of claim 1, wherein the patient receives a reduced amount of β blocker therapy during the second treatment phase.

~~4. The method of claim 3, wherein the reduced amount of β blocker therapy comprises a smaller dose of a β blocker.~~

~~5. The method of claim 3, wherein the reduced amount of β blocker therapy comprises a less frequent dose of a β blocker.~~

~~6. The method of claim 1, comprising transitioning from the first treatment phase to the second treatment phase when the patient achieves a therapeutically effective steady state of the myosin inhibitor.~~

~~7. The method of claim 6, wherein the steady state is achieved when the patient achieves a dose amount with no significant change in efficacy.~~

8. The method of claim 6, wherein the steady state is achieved in the time period of about 4 to 5 times the half life of the myosin inhibitor following administration of the myosin inhibitor.

9. The method of claim 6, wherein the steady state is achieved in the time period of about 4.5 times the half life of the myosin inhibitor following administration of the myosin inhibitor.

10. The method of claim 7, wherein the patient achieves the steady state when the patient achieves a dose amount wherein the patient's Valsalva or post-exercise LVOT gradient remains below 30 mmHg.

11. The method of claim 10, wherein the patient achieves the steady state when the patient achieves a dose amount wherein the patient's Valsalva or post-exercise LVOT gradient remains below 30 mmHg and ejection fraction remains above 50%.

12. The method of any one of claims 1-11, wherein the first treatment phase is about 4 weeks to about 28 weeks.

13. The method of claim 12, wherein the first treatment phase is about 24 weeks.

14. The method of claim 1, comprising transitioning from the first treatment phase to the second treatment phase when the patient achieves a Valsalva or post-exercise LVOT gradient below 30 mmHg.

15. The method of claim 14, comprising transitioning from the first treatment phase to the second treatment phase when the patient achieves a Valsalva or post-exercise LVOT gradient below 30 mmHg and an ejection fraction is above 50%.

16. The method of claim 1, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof, the method comprising transitioning from the first treatment phase to the second treatment phase when the patient achieves a trough blood plasma concentration of mavacamten of between 350 and 700 ng/mL.

17. The method of any one of claims 1-5 or 14-16, wherein the first treatment phase is about 4 weeks to about 28 weeks.

~~18. The method of claim 17, wherein the first treatment phase is about 4-6 weeks, wherein the steady state dose is about 5 mg per day of mavacamten.~~

~~19. The method of claim 17, wherein the first treatment phase is about 14 weeks.~~

~~20. The method of claim 1, comprising transitioning from the first treatment phase to the second treatment phase when the patient experiences a side effect due to β blocker therapy.~~

~~21. The method of claim 20, wherein the side effect is fatigue, orthostatic hypertension, erectile dysfunction, or any combination thereof.~~

~~22. The method of claim 1, comprising transitioning from the first treatment phase to the second treatment phase when a clinician deems necessary to discontinue or reduce the amount of β blocker therapy.~~

~~23~~4. The ~~method~~ use of any preceding claim, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.

~~24~~5. The ~~method~~ use of any preceding claim, wherein the patient has hypertrophic cardiomyopathy (HCM).

~~25~~6. The ~~method~~ use of any preceding claim, wherein the patient has obstructive hypertrophic cardiomyopathy (oHCM).

~~26~~7. The ~~method~~ use of any preceding claim, wherein the patient has non-obstructive hypertrophic cardiomyopathy (nHCM).

~~27~~8. The ~~method~~ use of any preceding claim, wherein the patient has heart failure with preserved ejection fraction (HFpEF).

~~28. The method of any preceding claim, wherein the patient is not suffering from one or more of, or is not suffering from any of: coronary artery disease (CAD), chest pain, angina, super ventricular arrhythmia, atrial fibrillation, congestive heart failure, left ventricular failure, stress cardiomyopathy, cardiac hypertension, ventricular tachycardia (VT), valvular disease, aortic stenosis, and coronary heart disease.~~

~~29. The method of any preceding claim, wherein the patient is not suffering from atrial fibrillation.~~

~~30. The method of any preceding claim, wherein the patient is not suffering from coronary artery disease (CAD).~~

~~31. The method of any preceding claim, wherein the β blocker therapy comprises administration of one or more β blockers selected from the group consisting of acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, nebivolol, propranolol, and sotalol.~~

~~32. The method of any preceding claim, wherein the peak exercise capacity of the patient is increased and/or maximized.~~

~~33. The method of any preceding claim, wherein the patient achieves an improvement in pVO_2 of at least about 2.2 mL/kg/min.~~

~~34. The method of any preceding claim, wherein the patient achieves (i) an improvement of at least 1.5 mL/kg/min in pVO_2 and a reduction of 1 or more NYHA Class, or (ii) an improvement of at least 3.0 mL/kg/min in pVO_2 with no worsening in NYHA Class.~~

~~35. The method of any preceding claim, wherein the patient has an ejection fraction >55% prior to beginning the first treatment phase.~~

~~36. The method of any preceding claim, wherein the patient has an E/e' >14 prior to beginning the first treatment phase.~~

~~37. The method of any preceding claim, wherein the patient has a left ventricular wall thickness ≥15mm or ≥13 mm with family history of HCM prior to beginning the first treatment phase.~~

~~38. The method of any preceding claim, wherein the patient with cardiac hypercontractility has ejection fraction of >55% and evidence of oHCM, HCM and/or heart failure symptoms prior to beginning the first treatment phase.~~

~~39.~~ Use of a myosin inhibitor in the manufacture of a medicament for the treatment of~~A method of treating~~ a patient having cardiac hypercontractility, impaired cardiac relaxation and/or left ventricular hypertrophy, wherein the patient is undergoing β blocker therapy, ~~the method comprising:~~

wherein~~discontinuing~~ the β blocker therapy is discontinued or reduced in amount~~or reducing the amount of β blocker therapy~~; and

~~administering to the patient~~wherein a therapeutically effective amount of a myosin inhibitor is to be administered to the patient.

~~40~~10. The ~~method~~ use of claim ~~39~~, ~~comprising discontinuing~~wherein the β blocker therapy is discontinued.

~~41~~11. The ~~method~~ use of claim ~~39~~, ~~comprising reducing~~wherein the amount of β blocker therapy is reduced.

~~42. The method of claim 41, wherein reducing the amount of β blocker therapy comprises reducing the dose of a β blocker.~~

~~43. The method of claim 41, wherein reducing the amount of β blocker therapy comprises reducing the frequency of dosing of a β blocker.~~

~~44~~12. The ~~method~~ use of any one of claims ~~39~~-~~43~~11, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.

~~45~~13. The ~~method~~use of claim ~~44~~12, wherein the administration of a therapeutically effective amount of a myosin inhibitor~~administering~~ to the patient ~~a therapeutically effective amount of a myosin inhibitor~~ comprises administration of~~administering~~ a starting dose of 5 mg of mavacamten per day.

~~46~~14. The ~~method~~ use of claim ~~45~~13, wherein the starting dose of 5 mg of mavacamten per day is adjusted or maintained based on the Valsalva or post-exercise LVOT gradient of the patient.

~~47~~15. The ~~method~~ use of claim ~~46~~14, wherein the starting dose of mavacamten is reduced to 2.5 mg if the Valsalva or post-exercise LVOT gradient of the patient is less than 30 mmHg.

~~48~~16. The ~~method~~ use of claim ~~47~~15, wherein the starting dose of mavacamten is reduced to 2.5 mg if the Valsalva or post-exercise LVOT gradient of the patient is less than 30 mmHg after 8 weeks of administering 5 mg of mavacamten per day.

~~49~~17. The ~~method~~ use of claim ~~46~~14, wherein the starting dose of mavacamten is increased to 10 mg if the Valsalva or post-exercise LVOT gradient of the patient is greater than or equal to 30 mmHg.

~~50~~18. The ~~method~~ use of claim ~~49~~17, wherein the starting dose of mavacamten is increased to 10 mg if the Valsalva or post-exercise LVOT gradient of the patient is greater than or equal to 30 mmHg after 8 weeks of administering 5 mg of mavacamten per day.

~~51~~19. The ~~method~~ use of any one of claims ~~39~~-~~50~~18, wherein the patient has hypertrophic cardiomyopathy (HCM).

~~52~~20. The ~~method~~ use of claim ~~5~~19, wherein the patient has obstructive hypertrophic cardiomyopathy (oHCM).

~~53~~21. The ~~method~~ use of claim ~~51~~19, wherein the patient has non-obstructive hypertrophic cardiomyopathy (nHCM).

~~54~~22. The ~~method~~ use of any one of claims ~~39~~-~~50~~18, wherein the patient has heart failure with preserved ejection fraction (HFpEF).

~~55~~23. The ~~method~~ use of any one of claims ~~39~~-22~~54~~, wherein the patient is not suffering from one or more of, or is not suffering from any of: coronary artery disease (CAD), chest pain, angina, super ventricular arrhythmia, atrial fibrillation, congestive heart failure, left ventricular failure, stress cardiomyopathy, cardiac hypertension, ventricular tachycardia (VT), valvular disease, aortic stenosis, and coronary heart disease.

~~56. The method of claim 55, wherein the patient is not suffering from atrial fibrillation.~~

~~57. The method of claim 55 or 56, wherein the patient is not suffering from coronary artery disease (CAD).~~

~~58~~24. The ~~method~~ use of any one of claims ~~39~~-~~57~~23, wherein the β blocker therapy comprises administration of one or more β blockers selected from the group consisting of acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, nebivolol, propranolol, and sotalol.

~~59~~25. The ~~method~~ use of any one of claims ~~39~~-~~58~~24, wherein the peak exercise capacity of the patient is increased and/or maximized.

6026. The usemethod of any one of claims 39-2559, wherein the patient achieves an improvement in pVO_2 of at least about 2.2 mL/kg/min.

6127. The method use of any one of claims 39-6026, wherein the patient achieves (i) an improvement of at least 1.5 mL/kg/min in pVO_2 and a reduction of 1 or more NYHA Class, or (ii) an improvement of at least 3.0 mL/kg/min in pVO_2 with no worsening in NYHA Class.

6228. The method use of any one of claims 39-6127, wherein the patient has one or more of:

an ejection fraction >55% prior to administration of the myosin inhibitor;

an E/e' >14 prior to administration of the myosin inhibitor; and

a left ventricular wall thickness ≥15mm or ≥13 mm with family history of HCM prior to administration of the myosin inhibitor.

~~63. The method of any one of claims 39-62, wherein the patient has an E/e' >14 prior to administration of the myosin inhibitor.~~

~~64. The method of any one of claims 39-63, wherein the patient has a left ventricular wall thickness ≥15mm or ≥13 mm with family history of HCM prior to administration of the myosin inhibitor.~~

6529. The method use of any one of claims 39-6428, wherein the patient with cardiac hypercontractility has ejection fraction of >55% and evidence of oHCM, HCM and/or heart failure symptoms prior to beginning the first treatment phase.

6630. Use of a myosin inhibitor in the manufacture of a medicament for the treatment of ~~A method of treating~~ a patient having cardiac hypercontractility, impaired cardiac relaxation and/or left ventricular hypertrophy, wherein the patient is not undergoing β blocker therapy, ~~the method comprising:~~

~~administering to~~wherein the patient is to be administered a therapeutically effective amount of a myosin inhibitor.

6731. The method use of claim 3066, wherein the patient has never received β blocker therapy.

~~68~~32. The ~~method~~ use of claim ~~66~~30, wherein the patient has previously received β blocker therapy but has not received β blocker therapy for at least 14 days prior to administration of the myosin inhibitor.

~~69~~33. The ~~method~~ use of claim ~~66~~30, wherein the patient has previously received β blocker therapy but has not received β blocker therapy for at least 30, at least 60, or at least 90 days prior to administration of the myosin inhibitor.

34~~70~~. The ~~method~~ use of any one of claims ~~66~~30-33~~69~~, wherein the patient is an athlete or has an active lifestyle.

35~~71~~. The ~~method~~ use of any one of claims ~~66~~30-34~~70~~, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.

~~72. The method of any one of claims 66-71, wherein the patient has hypertrophic cardiomyopathy (HCM).~~

~~73. The method of claim 72, wherein the patient has obstructive hypertrophic cardiomyopathy (oHCM).~~

~~74. The method of claim 72, wherein the patient has non-obstructive hypertrophic cardiomyopathy (nHCM).~~

~~75. The method of any one of claims 66-71, wherein the patient has heart failure with preserved ejection fraction (HFpEF).~~

~~76. The method of any one of claims 66-75, wherein the patient is not suffering from one or more of, or is not suffering from any of: coronary artery disease (CAD), chest pain, angina, super ventricular arrhythmia, atrial fibrillation, congestive heart failure, left ventricular failure, stress cardiomyopathy, cardiac hypertension, ventricular tachycardia (VT), valvular disease, aortic stenosis, and coronary heart disease.~~

~~77. The method of claim 76, wherein the patient is not suffering from atrial fibrillation.~~

~~78. The method of claim 76 or 77, wherein the patient is not suffering from coronary artery disease (CAD).~~

79. The method of any one of claims 66-78, wherein the β blocker therapy comprises administration of one or more β blockers selected from the group consisting of acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, nebivolol, propranolol, and sotalol.

80. The method of any one of claims 66-79, wherein the peak exercise capacity of the patient is increased and/or maximized.

81. The method of any one of claims 66-80, wherein the patient achieves an improvement in pVO_2 of at least about 2.2 mL/kg/min.

82. The method of any one of claims 66-81, wherein the patient achieves (i) an improvement of at least 1.5 mL/kg/min in pVO_2 and a reduction of 1 or more NYHA Class, or (ii) an improvement of at least 3.0 mL/kg/min in pVO_2 with no worsening in NYHA Class.

83. The method of any one of claims 66-82, wherein the patient has an ejection fraction >55% prior to administration of the myosin inhibitor.

84. The method of any one of claims 66-83, wherein the patient has an E/e' >14 prior to administration of the myosin inhibitor.

85. The method of any one of claims 66-84, wherein the patient has a left ventricular wall thickness ≥15mm or ≥13 mm with family history of HCM prior to administration of the myosin inhibitor.

86. The method of any one of claims 66-85, wherein the patient with cardiac hypercontractility has ejection fraction of >55% and evidence of oHCM, HCM and/or heart failure symptoms prior to beginning the first treatment phase.