Claims

We claim:

~~1. A method for treating a disease in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a myosin modulator, wherein the subject has (a) an elevated level of cardiac troponin and/or (b) an elevated NT-proBNP or BNP.~~

~~2. The method of claim 1, wherein the cardiac troponin is cardiac troponin I (cTnI) or cardiac troponin T (cTnT).~~

~~3. The method of claim 2, wherein the subject further has normal systolic contractility or systolic hypercontractility, wherein the left ventricular ejection fraction of the subject is >50%.~~

~~4. The method of any one of claims 1-3, wherein the subject is suffering from a symptom of a cardiovascular disease.~~

~~5. The method of any one of the preceding claims, wherein the symptom is selected from the group consisting of shortness of breath, dizziness, chest pain, syncope, or a limit on an activity of daily living.~~

~~6. The method of claim 5, wherein the limit on an activity of daily living is selected from the group consisting of a limit on personal care, mobility, or eating.~~

~~7. The method of any one of the preceding claims, wherein the subject has any one or combination of myocardial diastolic dysfunction, an elevated left ventricular filling pressure, left ventricular hypertrophy and left atrium enlargement (LAE).~~

~~8. The method of any one of the preceding claims, wherein the subject further has an elevated E/e'.~~

~~9. The method of any one of the preceding claims, wherein the subject has a normal or hypercontractile left ventricle ejection fraction (LVEF).~~

~~10. The method of claim 9, wherein the normal LVEF is between 52-74%.~~

~~11. The method of any one of the preceding claims, wherein the subject is suffering from diastolic dysfunction, left ventricular hypertrophy, malignant left ventricular hypertrophy, angina, ischemia, hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), or heart failure with preserved ejection fraction (HFpEF).~~

~~12. The method of any one of the preceding claims wherein the subject is suffering from valvular aortic stenosis, mixed LV systolic and diastolic dysfunction, Idiopathic RV hypertrophy, Chronic kidney disease, aortic insufficiency, tetralogy of Fallot, mitral stenosis, Noonan Syndrome, or acute coronary syndrome.~~

~~13. The method of any one of the preceding claims, wherein the subject is diagnosed with an HCM.~~

~~14. The method of claim 13, wherein HCM is obstructive HCM.~~

~~15. The method of claim 13, wherein the HCM is non-obstructive HCM.~~

~~16. The method of any one of the preceding claims, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~17. The method of any one of the preceding claims, wherein the subject experiences a reduction in the risk of a major cardiovascular event, wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~18. The method according to any one of the preceding claims, wherein the subject experiences a statistically significant reduction in their level(s) of cardiac troponin and/or NT-proBNP or BNP.~~

~~19. A method for treating a disease in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a myosin inhibitor, wherein the subject is suffering from a disease comprising oHCM, nHCM, HFpEF, diastolic dysfunction, left ventricular hypertrophy (LVH), malignant LVH, ischemia, or angina, or suffering from a disease comprising valvular aortic stenosis, mixed LV systolic and diastolic dysfunction, Idiopathic RV hypertrophy, Chronic kidney disease, aortic insufficiency, tetralogy of Fallot, mitral stenosis, Noonan Syndrome, or acute coronary syndrome, comprising the steps of:~~

~~recommending the subject be tested for elevated cardiac troponin levels and/or elevated NT-proBNP or BNP levels; and~~

~~administering to the subject a therapeutically effective amount of a myosin inhibitor if the subject has (a) elevated cardiac troponin levels and/or (b) elevated NT-proBNP or BNP levels.~~

~~20. The method of claim 19, wherein cardiac troponin measured is cTnI or cTnT.~~

~~21. The method of claim 19, further comprising the step of recommending the subject be tested for elevated NT-proBNP or BNP levels and then administering the myosin inhibitor if elevated cardiac troponin levels and elevated NT-proBNP or BNP levels are observed.~~

~~22. The method of any one of claims 19-21, further comprising the step of recommending the subject be evaluated for elevated E/e' and then administering the myosin inhibitor if elevated E/e' is observed.~~

~~23. The method of any one of claims 19-22, wherein the disease in the subject is diagnosed in accordance with the New York Heart Association (NYHA) classification.~~

~~24. The method of claim 23, further comprising the step of: assessing a NYHA classification score of the subject before and after administration of the therapeutically effective amount of a myosin inhibitor, wherein a decreased NYHA score after administration of the myosin inhibitor indicates a reduction in the extent of the disease in the subject.~~

~~25. The method of claim 23, further comprising the step of administering a myosin inhibitor until the subject has moved from a Class III to Class II, or Class II to Class I NYHA classification.~~

~~26. The method of any one of claims 19-25, wherein the NYHA classification score of the subject after administration of the therapeutically effective amount of a myosin inhibitor decreases from Class III to Class II, or from Class II to Class I.~~

~~27. The method of any one of claims 19-22, wherein the disease in the subject is diagnosed in accordance with the Kansas City Cardiomyopathy Questionnaire (KCCQ) score.~~

~~28. The method of claim 27, furthering comprising the step of: determining a KCCQ score of the subject before and after administration of the therapeutically effective amount of a myosin inhibitor, wherein an increased KCCQ score after administration of the myosin inhibitor indicates a reduction in the extent of the disease in the subject.~~

~~29. The method of any one of claims 19-28, further comprising assessing peak oxygen consumption (VO_2) and/or VE/CO_2 or VE/VCO_2 slope in the subject during exercise before and after administration of the therapeutically effective amount of a myosin inhibitor, wherein an increase in peak oxygen consumption in the subject after administration of the myosin inhibitor indicates a reduction in the extent of HCM or the at least one symptomatic component or condition thereof in the subject.~~

~~30. The method of any one of claims 19-29, wherein the subject has been diagnosed as eligible for surgical intervention or percutaneous ablation for treating the disease.~~

~~31. The method of any one of claims 19-29, wherein the subject has a LVEF > 50%.~~

~~32. The method of claim 30, wherein the disease is non-obstructive HCM.~~

~~33. The method of any one of claims 19-32, wherein the myosin modulator is a myosin inhibitor.~~

~~34. The method of claim 33, wherein the myosin inhibitor is mavacamten or a pharmaceutical acceptable salt thereof.~~

~~35. The method of any one of the preceding claims, wherein the subject experiences a reduction in the risk of a major cardiovascular event, wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~36. The method of any one of the preceding claims, wherein the subject experiences a statistically significant reduction in their level(s) of (a) cardiac troponin and/or (b) NT-proBNP or BNP.~~

~~37. A method of reducing mortality in a subject suffering from a symptom due to a cardiovascular disease, comprising administering to the subject a therapeutically effective starting amount of a myosin modulator to achieve a stable desired clinical state, followed by administering a reduced dosage regimen of the myosin inhibitor to maintain or improve the desired clinical state.~~

~~38. The method of claim 37, wherein the symptom due to a cardiovascular disease is shortness of breath, dizziness, chest pain, syncope, fatigue, or limits on activities of daily living.~~

~~39. The method of claim 38, wherein the limit on an activity of daily living is selected from the group consisting of a limit on personal care, mobility, or eating.~~

~~40. The method of claim 37, wherein the cardiovascular disease is selected from the group consisting of oHCM, nHCM, HFpEF, LVH, malignant LVH, ischemia or angina.~~

~~41. The method of claim any of claims 37-40 wherein the myosin modulator is a myosin inhibitor.~~

~~42. The method of claim 41, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~43. The method of claim 42, wherein the reduced daily dosage regimen is about 3 times, 4 times, or 5 times less than the amount of mavacamten needed to maintain a blood plasma level of mavacamten in the subject.~~

~~44. The method of claim 43, wherein the blood plasma level of mavacamten is between 200 to 750 ng/mL.~~

~~45. The method of any of claims 37-44, wherein the reduced dosage regimen is less than 5 mg per day, 4 mg or less per day, 3 mg or less per day, 2 mg or less per day, or 1 mg or less per day.~~

~~46. The method of claim 42, wherein the therapeutically effective amount of mavacamten is from about 5 mg to about 15 mg, and the reduced dosage regimen is less than 5 mg of mavacamten per day.~~

~~47. The method of any one of claims 37-46, wherein the reduced dosage regimen is administered to the subject chronically.~~

~~48. The method of any one of the preceding claims, wherein the patient is suffering from a disease selected from the group consisting of oHCM, nHCM, HFpEF, LVH or ischemia.~~

~~49. The method of any one of the preceding claims, wherein the subject experiences a reduction in the risk of a major cardiovascular event.~~

~~50. The method of any one of the preceding claims, wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~51. A method of treating a subject after septal reduction therapy (SRT), comprising administering to the subject a reduced dosage regimen of the myosin modulator to maintain a stable desired clinical state after septal reduction therapy.~~

~~52. The method of claim 51, wherein the myosin modulator is a myosin inhibitor.~~

~~53. The method of claim 51, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~54. The method of 53, wherein the reduced dosage regimen is a daily amount of mavacamten to achieve between 50 to 350 ng/ml plasma concentration or less than 5 mg per day, 4 mg or less per day, 3 mg or less per day, 2.5 mg or less per day, or 1 mg or less per day.~~

~~55. A method of preventing HCM or LVH in a subject at risk of developing HCM or LVH, comprising and the step of administering to the at risk subject in need thereof a myosin modulator , wherein the subject has (a) an elevated cardiac troponin level and/or (b) an elevated NT-proBNP or BNP level.~~

~~56. The method of claim 55, wherein the at risk subject further has an elevated NT-proBNP or BNP level.~~

~~57. The method of claims 55 or 56, wherein the myosin modulator is a myosin inhibitor.~~

~~58. The method of claim 57, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~59. The method of any one of claims 55-58 wherein the HCM is oHCM or nHCM.~~

~~60. The method of any one of claims 55-58, wherein the subject has Noonan Syndrome.~~

~~61. The method of any one of claims 55-60, wherein the subject is a child, adolescent, or adult.~~

~~62. A method of preventing HCM or LVH in a subject at risk of developing HCM or LVH, comprising and the step of administering to the subject in need thereof a low dose of a myosin modulator to completely or partially prevent development of HCM or LVH.~~

~~63. The method of claims 62, wherein the myosin modulator is a myosin inhibitor.~~

~~64. The method of claim 63, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof, which is administered chronically.~~

~~65. The method of claim 62-64, wherein the subject to be treated is a child, an adolescent or an adult.~~

~~66. The method of any one of claims 55-65, wherein the subject has a symptom of a HCM or LVH comprising shortness of breath, dizziness, chest pain, syncope, fatigue and limits on activities of daily living.~~

~~67. The method of claim 66, wherein the limit on an activity of daily living is selected from the group consisting of a limit on personal care, mobility, or eating.~~

~~68. The method of any one of claims 62-67, wherein the low dose of the myosin inhibitor is an amount that is 3 to 5 times less than the amount needed for such myosin inhibitor to reduce the LVOT gradient in an oHCM patient.~~

~~69. The method of any one of claims 62-68, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~70. The method of claim 69, wherein the low dose of mavacamten is less than 5 mg per day or is a mount to maintain the blood plasma concentration of mavacamten between 50 to 350 ng/mL.~~

~~71. The method of claim 69, wherein the low dose of mavacamten is 1 mg, 2 mg, 2.5 mg, or 3 mg per day.~~

~~72. The method of any one of claims 62-71, wherein the dosage regimen of a myosin inhibitor is administered to the subject at an early stage of development of HCM or LVH.~~

~~73. The method of claim 72, wherein HCM is oHCM or nHCM.~~

~~74. A method of reducing an adverse event in a subject related to reduced cardiac output following a treatment comprising a myosin inhibitor, comprising the step of administering to the subject a therapeutic dose of a beta adrenergic agonist.~~

~~75. The method of claim 74, wherein the beta adrenergic agonist is dobutamine.~~

~~76. The method of claim 74, wherein the beta adrenergic agonist is levosimendan.~~

~~77. The method of claim 75, wherein the therapeutic dose of the beta adrenergic agonist is from about 5 μg/kg/min to about 10 μg/kg/min dobutamine infusion.~~

~~78. The method of claim 76, wherein the therapeutic dose of the beta adrenergic agonist is infusion of from about 0.2 to about 0.4 μmol/kg of levosimendan over a period of about 30 minutes.~~

~~79. The method of any one of claims 74-78, further comprising the additional step of administering to the subject an intravenous volume supplementation and/or an arterial vasoconstrictor agent.~~

~~80. The method of claim 79, wherein the arterial vasoconstrictor agent is an adrenergic agonist.~~

~~81. The method of any one of claims 74-80, wherein the myosin inhibitor is mavacamten.~~

~~82. The method of claim 74, further comprising monitoring the blood plasma concentration of mavacamten in the subject and determining that the subject has received a supratherapeutic dose of mavacamten based on the measured blood plasma concentration.~~

~~83. The method of claim 82, wherein the supratherapeutic dose of mavacamten is a dose of mavacamten that causes a blood plasma concentration of mavacamten of greater than about 1000 ng/mL in the subject.~~

~~84. The method of any one of claims 1-83, wherein the myosin inhibitor is mavacamten.~~

~~85. The method of claim 84, wherein mavacamten is crystalline Form A of mavacamten.~~

~~86. A method for treating a disease in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a myosin modulator, wherein the subject has an elevated level of cardiac troponin and/or an elevated E/e'.~~

~~87. The method of claim 86, wherein the cardiac troponin is cardiac troponin I (cTnI) or cardiac troponin T (cTnT).~~

~~88. The method of claim 87, wherein the cardiac troponin is cTnI or high sensitivity cTnI (hs-cTnI).~~

~~89. The method of any one of claims 86-88, wherein the subject is suffering from a symptom of a cardiovascular disease.~~

~~90. The method of claim 89, wherein the symptom is selected from the group consisting of shortness of breath, dizziness, chest pain, syncope, or a limit on an activity of daily living.~~

~~91. The method of claim 90, wherein the limit on an activity of daily living is selected from the group consisting of a limit on personal care, mobility, or eating.~~

~~92. The method of any one of claims 86-91, wherein the subject further has an elevated NT-proBNP or BNP level.~~

~~93. The method of any one of claims 86-92, wherein the subject has an elevated E/e'.~~

~~94. The method of any one of claims 86-93, wherein the subject has a normal or hypercontractile left ventricle ejection fraction (LVEF).~~

~~95. The method of claim 94, wherein the normal LVEF is between 52-74%.~~

~~96. The method of any one of claims 86-95, wherein the subject is suffering from diastolic dysfunction, left ventricular hypertrophy (LVH), malignant LVH, angina, ischemia, hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), or heart failure with preserved ejection fraction (HFpEF).~~

~~97. The method of claim 96, wherein the subject is diagnosed with HFpEF.~~

~~98. The method of claim 97, wherein the subject is diagnosed with HCM.~~

~~99. The method of claim 98, wherein HCM is obstructive HCM.~~

~~100. The method of claim 98, wherein the HCM is non-obstructive HCM.~~

~~101. The method of claims 86-100, wherein the myosin modulator is a myosin inhibitor.~~

~~102. The method of claim 101, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~103. The method of claims 86-102, wherein the subject experiences a reduction in the risk of a major cardiovascular event, wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~104. The method according to any one of claims 86-103, wherein the subject experiences a statistically significant reduction in their level(s) of cardiac troponin and/or NT-proBNP or BNP.~~

~~105. A method for treating a disease in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a myosin inhibitor, wherein the subject is suffering from a disease comprising oHCM, nHCM, HFpEF, diastolic dysfunction, left ventricular hypertrophy (LVH), malignant LVH, ischemia, or angina, comprising the steps of:~~

~~recommending the subject to be tested for elevated cardiac troponin levels and/or elevated E/e'; and~~

~~administering to the subject a therapeutically effective amount of a myosin inhibitor if the subject has elevated cardiac troponin levels and/or elevated E/e'.~~

~~106. The method of claim 105, wherein cardiac troponin measured is cTnI or cTnT.~~

~~107. The method of claim 105, further comprising the step of recommending the subject be tested for elevated E/e' and then administering the myosin inhibitor if elevated cardiac troponin levels and elevated E/e' are observed.~~

~~108. The method of any one of claims 105-107, further comprising the step of recommending the subject be evaluated for elevated NT-proBNP or BNP and then administering the myosin inhibitor if elevated cardiac troponin levels, elevated NT-proBNP or BNP levels, and elevated E/e' are observed.~~

~~109. The method of any one of claims 105-108, wherein the disease in the subject is diagnosed in accordance with the New York Heart Association (NYHA) classification.~~

~~110. The method of claim 109, further comprising the step of: assessing a NYHA classification score of the subject before and after administration of the therapeutically effective amount of a myosin inhibitor, wherein a decreased NYHA score after administration of the myosin inhibitor indicates a reduction in the extent of the disease in the subject.~~

~~111. The method of claim 109, further comprising the step of administering a myosin inhibitor until the subject has moved from a Class III to Class II, or Class II to Class I NYHA classification.~~

~~112. The method of any one of claims 105-111, wherein the NYHA classification score of the subject after administration of the therapeutically effective amount of a myosin inhibitor decreases from Class III to Class II, or from Class II to Class I.~~

~~113. The method of any one of claims 105-108, wherein the disease in the subject is diagnosed in accordance with the Kansas City Cardiomyopathy Questionnaire (KCCQ) score.~~

~~114. The method of claim 113, furthering comprising the step of: determining a KCCQ score of the subject before and after administration of the therapeutically effective amount of a myosin inhibitor, wherein an increased KCCQ score after administration of the myosin inhibitor indicates a reduction in the extent of the disease in the subject.~~

~~115. The method of any one of claims 105-114, further comprising assessing peak oxygen consumption (VO2) and/or VE/VCO_2 slope in the subject during exercise before and after administration of the therapeutically effective amount of a myosin inhibitor, wherein the peak oxygen consumption (VO2) in the subject increases.~~

~~116. The method of any of claims 105-115, wherein the disease is HFpEF.~~

~~117. The method of any of claims 105-115, wherein the disease is obstructive HCM.~~

~~118. The method of any one of claims 105-115, wherein the disease is non-obstructive HCM.~~

~~119. The method of any one of claims 105-118, wherein the myosin inhibitor is mavacamten, or a pharmaceutically acceptable salt thereof.~~

~~120. The method of any one of claims 105-119, wherein the subject experiences a reduction in the risk of a major cardiovascular event, e.g., wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~121. The method of any one of claims 105-120, wherein the subject experiences a statistically significant reduction in their level(s) of (a) cardiac troponin and/or (b) NT-proBNP or BNP.~~

~~121. The method of any one of claims 105-121, wherein after administration of the therapeutically effective amount of a myosin inhibitor, the subject experiences an improvement in pVO_2 and optionally an improvement in NYHA Class, for example:~~

~~(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.~~

~~122. A method of administering mavacamten or a pharmaceutically acceptable salt thereof to a subject suffering from HFpEF, comprising:~~

~~administering a first dose of mavacamten or a pharmaceutically acceptable salt thereof to the subject having an elevated NT-proBNP level, and/or an elevated cTnT, and/or an elevated cTnI;~~

~~measuring a second NT-proBNP or BNP level in the subject;~~

~~if the second NT-proBNP or BNP level is not at least 15-75% less than the first NT-proBNP or BNP level, then administering a second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during a second treatment period; and~~

~~if the second NT-proBNP or BNP level is at least 15-75% less than the first NT-proBNP or BNP level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during a second treatment period.~~

~~123. The method of claim 122, comprising:~~

~~if the second NT-proBNP or BNP level is not at least 40-60% less than the first NT-proBNP or BNP level, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second NT-proBNP or BNP level is at least 40-60% less than the first NT-proBNP or BNP level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~124. The method of claim 123, comprising:~~

~~if the second NT-proBNP or BNP level is not at least 50% less than the first NT-proBNP or BNP level, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second NT-proBNP or BNP level is at least 50% less than the first NT-proBNP or BNP level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~125. The method of any one of claims 122-124, wherein the subject has an elevated level of NT-proBNP or BNP.~~

~~126. The method of claim 125, wherein the first NT-proBNP or BNP level is an elevated level.~~

~~127. The method of any one of claims 122-126, further comprising measuring a first LVEF of the subject, and measuring a second LVEF of the subject after the first LVEF and after the start of the first treatment period.~~

~~128. The method of claim 127, further comprising measuring the second LVEF at the end of, after, or within four weeks before the end of, the first treatment period.~~

~~129. The method of claim 127 or 128, wherein:~~

~~if the second NT-proBNP or BNP level is not at least 15-75% less than the first NT-proBNP or BNP level and the second LVEF is not at least 10-20% less than the first LVEF, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second NT-proBNP or BNP level is at least 15-75% less than the first NT-proBNP or BNP level or the second LVEF is at least 10-20% less than the second LVEF, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~130. The method of claim 129, wherein:~~

~~if the second NT-proBNP or BNP level is not at least 40-60% less than the first NT-proBNP or BNP level and the second LVEF is not at least 10-20% less than the first LVEF, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second NT-proBNP or BNP level is at least 40-60% less than the first NT-proBNP or BNP level or the second LVEF is at least 10-20% less than the second LVEF, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~131. The method of claim 130, wherein:~~

~~if the second NT-proBNP or BNP level is not at least 50% less than the first NT-proBNP or BNP level and the second LVEF is not at least 15% less than the first LVEF, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second NT-proBNP or BNP level is at least 50% less than the first NT-proBNP or BNP level or the second LVEF is at least 15% less than the second LVEF, then administering the~~

~~first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~132. The method of any one of claims 122-130, wherein the first NT-proBNP or BNP level is measured before the first treatment period.~~

~~133. The method of claim 132, wherein the first NT-proBNP or BNP level is measured immediately before, or within two weeks before, the first treatment period.~~

~~134. The method of any one of claims 122-133, wherein the second NT-proBNP or BNP level is measured during the first treatment period.~~

~~135. The method of claim 133, wherein the second NT-proBNP or BNP level is measured at the end of, or within four weeks of the end of, the first treatment period.~~

~~136. A method of administering mavacamten or a pharmaceutically acceptable salt thereof to a subject suffering from with HFpEF, comprising:~~

~~measuring a first cardiac troponin level in the subject;~~

~~administering a first dose of mavacamten or a pharmaceutically acceptable salt thereof to the subject during a first treatment period;~~

~~measuring a second cardiac troponin level in the subject;~~

~~if the second cardiac troponin level is not at least 10-50% less than the first cardiac troponin level, then administering a second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during a second treatment period; and~~

~~if the second cardiac troponin level is at least 10-50% less than the first cardiac troponin level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during a second treatment period.~~

~~137. The method of claim 136, comprising:~~

~~if the second cardiac troponin level is not at least 20-40% less than the first cardiac troponin level, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second cardiac troponin level is at least 20-40% less than the first cardiac troponin level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~138. The method of claim 137, comprising:~~

~~if the second cardiac troponin level is not at least 30% less than the first cardiac troponin level, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second cardiac troponin level is at least 30% less than the first cardiac troponin level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~139. The method of any one of claims 136-138, wherein the subject has an elevated level of NT-proBNP or BNP.~~

~~140. The method of any one of claims 136-139, wherein the subject has an elevated level of cardiac troponin.~~

~~141. The method of any one of claims 136-140, wherein the cardiac troponin measured is cTnI or cTnT.~~

~~142. The method of claim 141, wherein the cardiac troponin level measured is hs-cTnI.~~

~~143. The method of any one of claims 136-142, further comprising measuring a first LVEF of the subject, and measuring a second LVEF of the subject after the first LVEF and after the start of the first treatment period.~~

~~144. The method of claim 143, further comprising measuring the second LVEF at the end of, after, or within two weeks before the end of, the first treatment period.~~

~~145. The method of claim 143 or 144, wherein:~~

~~if the second cardiac troponin level is not at least 10-50% less than the first cardiac troponin level and the second LVEF is not at least 10-20% less than the first LVEF, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second cardiac troponin level is at least 10-50% less than the first cardiac troponin level or the second LVEF is at least 10-20% less than the second LVEF, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~146. The method of claim 145, wherein:~~

~~if the second cardiac troponin level is not at least 20-40% less than the first cardiac troponin level and the second LVEF is not at least 10-20% less than the first LVEF, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second cardiac troponin level is at least 20-40% less than the first cardiac troponin level or the second LVEF is at least 10-20% less than the second LVEF, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~147. The method of claim 146, wherein:~~

~~if the second cardiac troponin level is not at least 30% less than the first cardiac troponin level and the second LVEF is not at least 15% less than the first LVEF, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second cardiac troponin level is at least 30% less than the first cardiac troponin level or the second LVEF is at least 15% less than the second LVEF, then administering the first~~

~~dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~148. The method of any one of 136-147, further comprising measuring a first NT-proBNP or BNP level of the subject, and measuring a second NT-proBNP or BNP level of the subject after the first NT-proBNP or BNP level and after the start of the first treatment period.~~

~~149. The method of claim 148, further comprising measuring the second NT-proBNP or BNP level at the end of, after, or within four weeks before the end of, the first treatment period.~~

~~150. The method of claim 148 or 149, wherein:~~

~~if the second cardiac troponin level is not at least 10-50% less than the first cardiac troponin level and the second NT-proBNP or BNP level is not more than 20-60% greater than the first NT-proBNP or BNP level, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~wherein if the second cardiac troponin level is at least 10-50% less than the first cardiac troponin level or the second NT-proBNP or BNP level is more than 20-60% greater than the first NT-proBNP or BNP level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~151. The method of claim 150, wherein:~~

~~if the second cardiac troponin level is not at least 20-40% less than the first cardiac troponin level and the second NT-proBNP or BNP level is not more than 40-55% greater than the first NT-proBNP or BNP level, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second cardiac troponin level is at least 20-40% less than the first cardiac troponin level or the second NT-proBNP or BNP level is more than 40-55% greater than the first NT-proBNP or BNP level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~152. The method of claim 156, wherein:~~

~~if the second cardiac troponin level is not at least 30% less than the first cardiac troponin level and the second NT-proBNP or BNP level is not more than 50% greater than the first NT-proBNP or BNP level, then administering the second dose of mavacamten or a pharmaceutically acceptable salt thereof that is greater than the first dose during the second treatment period; and~~

~~if the second cardiac troponin level is at least 30% less than the first cardiac troponin level or the second NT-proBNP or BNP level is more than 50% greater than the first NT-proBNP or BNP level, then administering the first dose of mavacamten or a pharmaceutically acceptable salt thereof during the second treatment period.~~

~~153. The method of any one of claims 136-152, wherein the first cardiac troponin level is measured before the first treatment period.~~

~~154. The method of claim 153, wherein the first cardiac troponin level is measured immediately before, or within two weeks before, the first treatment period.~~

~~155. The method of any one of claims 136-154, wherein the second cardiac troponin level is measured during the first treatment period.~~

~~156. The method of claim 155, wherein the second cardiac troponin level is measured at the end of, or within four weeks of the end of, the first treatment period.~~

~~157. The method of any one of claims 122-156, wherein the first dose is from about 1 mg to about 5 mg.~~

~~158. The method of claim 157, wherein the first dose is about 2.5 mg.~~

~~159. The method of any one of claims 122-158, wherein the second dose is from about 2.5 mg to about 10 mg.~~

~~160. The method of claim 159, wherein the second dose is about 5 mg.~~

~~161. The method of any one of claims 122-160, wherein the second dose is about 1.5 times to about 3 times the first dose.~~

~~162. The method of claim 161, wherein the second dose is about double the first dose.~~

~~163. The method of any one of claims 122-162, wherein the first dose is administered daily during the first treatment period.~~

~~164. The method of any one of claims 122-163, wherein the first treatment period is at least two weeks, at least four weeks, at least six weeks, at least eight weeks, at least ten weeks, at least twelve weeks, 4-20 weeks, 10-16 weeks, or about 14 weeks.~~

~~165. The method of any one of claims 122-164, wherein the second dose is administered daily during the second treatment period.~~

~~166. The method of any one of claims 122-165, wherein the second treatment period is at least two weeks, at least four weeks, at least six weeks, at least eight weeks, at least ten weeks, or at least twelve weeks.~~

~~167. The method of any one of claims 122-166, wherein the subject has prior objective evidence of heart failure as shown by one or more of:~~

~~previous hospitalization for heart failure with radiographic evidence of pulmonary congestion;~~

~~elevated left ventricular end-diastolic pressure or pulmonary capillary wedge pressure at rest or with exercise;~~

~~elevated level of NT-proBNP or BNP; and~~

~~echocardiographic evidence of medial E/e' ratio ≥15 or left atrial enlargement together with chronic treatment with a loop diuretic.~~

~~168. The method of any one of claims 122-167, wherein the subject has an elevated E/e'.~~

~~169. A method for treating a disease in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a myosin inhibitor, wherein the subject has an elevated level of cardiac troponin, and/or an elevated NT-proBNP or BNP, and/or an elevated E/e'.~~

~~170. The method of claim 169, wherein the cardiac troponin is cardiac troponin I (cTnI) or cardiac troponin T (cTnT).~~

~~171. The method of claim 170, wherein the cardiac troponin is cTnI or high sensitivity cTnI (hs-cTnI).~~

~~172. The method of claim 169, wherein the elevated troponin level is above the upper limit of normal (ULN).~~

~~173. The method of claim 172, wherein the ULN is about 0.014 ng/mL for cTnT.~~

~~174. The method of claim 172, wherein the ULN is about 47 pg/mL for cTnI.~~

~~175. The method of claim 169, wherein E/e' is greater than 10.~~

~~176. The method of claim 169, wherein E/e' is the average E/e'.~~

~~177. The method of claim 169, wherein E/e' is greater than 13.~~

~~178. The method of claim 169, wherein BNP is greater than 35 pg/mL.~~

~~179. The method of claim 169, wherein the NT-proBNP is greater than 125 pg/mL.~~

~~180. The method of claim 169, wherein NT-proBNP is greater than 250 pg/mL.~~

~~181. The method of claim 169, wherein NT-proBNP is greater than 300 pg/mL.~~

~~182. The method of claim 169, wherein NT-proBNP is greater than 450 pg/mL.~~

~~183. The method of claim 179, wherein the subject is 74 years old or younger.~~

~~184. The method of claim 182, wherein the subject is 75 years old or older.~~

~~185 The method of any one of claims 169-184, wherein the subject is suffering from a symptom of a cardiovascular disease.~~

~~186. The method of claim 185, wherein the symptom is selected from the group consisting of shortness of breath, dizziness, chest pain, syncope, or a limit on an activity of daily living.~~

~~187. The method of claim 185, wherein the limit on an activity of daily living is selected from the group consisting of a limit on personal care, mobility, or eating.~~

~~188. The method of any one of claims 169-187, wherein the subject is suffering from diastolic dysfunction, elevated filling pressure, elevated left ventricular filling pressure, left atrial enlargement, preserved systolic function, or systolic hyper-contractility.~~

~~189. The method of any one of claims 169-187, wherein the subject is suffering from hypertrophic cardiomyopathy (HCM).~~

~~190. The method of any one of claims 169-187, wherein the subject is suffering from left ventricular hypertrophy (LVH), malignant LVH, angina, ischemia, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy (RCM).~~

~~191. The method of any one of claims 169-187, wherein the subject is suffering from heart failure with preserved ejection fraction (HFpEF).~~

~~192. The method claim 191, wherein the subject is suffering from shortness of breath, fatigue, palpitations (atrial fibrillation), chest discomfort, or edema.~~

~~193. The method of claim 191, wherein the subject is suffering from myocardial diastolic dysfunction, elevated LV filing pressure, left ventricular wall hypertrophy, left atrial enlargement, normal or hypercontractility, myocardial injury and fibrosis, or abnormal myocardial energetics.~~

~~194. The method of claim 191, wherein the subject is suffering from reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, or ankle swelling.~~

~~195. The method of any one of claims 169-187, wherein the subject has a normal or hypercontractile left ventricle ejection fraction (LVEF).~~

~~196. The method of claim 195, wherein the normal LVEF is between 52-74%.~~

~~197. The method of any one of claims 169-187, wherein the subject is diagnosed with HCM.~~

~~198. The method of claim 197, wherein the HCM is obstructive HCM.~~

~~199. The method of claim 197, wherein the HCM is non-obstructive HCM.~~

~~200. The method of any one of claims 169-199, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~201. The method of any one of claims 169-197, wherein the subject experiences a reduction in the risk of a major cardiovascular event, e.g., wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~202. The method according to any one of claims 169-201, wherein the subject experiences a statistically significant reduction in their level(s) of (a) cardiac troponin, and/or (b) NT-proBNP or BNP, and/or (c) E/e'.~~

~~203. A method for treating a disease in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a myosin inhibitor, wherein the subject has a LVEF of greater than 52%, and one or more of an elevated level of (a) cardiac troponin, (b) NT-proBNP or BNP, and (c) elevated E/e'.~~

~~204. The method of claim 203, wherein the subject has preserved systolic function or normal or systolic hyper-contractility.~~

~~205. The method of claim 203, wherein treating the disease with the myosin inhibitor results in the subject experiencing a reduction in global longitudinal strain.~~

~~206. The method of claim 203, wherein the subject has diastolic dysfunction.~~

~~207. The method of claim 203, wherein treating the disease with the myosin inhibitor results in the subject experiencing a reduction in left ventricle filling pressures.~~

~~208. The method of claim 207, wherein the reduction is characterized by an improvement in the average E/e'.~~

~~209. The method of claim 203, wherein the subject has left ventricle hypertrophy or left atrium size enlargement.~~

~~210. The method of claim 209, wherein the subject has mild left ventricular hypertrophy.~~

~~211. The method of claims 209 or 210, wherein treating the disease with the myosin inhibitor results in the subject experiencing a reduction left ventricular mass, left ventricular wall thickness, interventricular septal thickness, or left ventricular septal thickness.~~

~~212. The method of any of claims 203-211, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~213. The method of claim 212, wherein the therapeutically effective amount is from about 2.5 mg to about 15 mg.~~

~~214. The method of claim 213, wherein the therapeutically effective amount is from about 2.5 mg to about 5 mg per day.~~

~~215. The method of claim 213, wherein the therapeutically effective amount is from about 5 mg to about 7.5 mg per day.~~

~~216. The method of claim 213, wherein the therapeutically effective amount is from about 7.5 mg to about 15 mg per day.~~

~~217. The method of any one of claims 203-216, wherein the cardiac troponin is cardiac troponin T (cTnT).~~

~~218. The method of claim 217, wherein the cardiac troponin is cardiac cTnI or high sensitivity cTnI (hs-cTnI).~~

~~219. The method of any one of claims 203-216, wherein elevated E/e' is greater than 10 or 13.~~

~~220. The method of any one of claims 203-216, wherein E/e' is the average E/e'.~~

~~221. The method of any one of claims 203-216, wherein BNP is greater than 35 pg/mL.~~

~~222. The method of any one of claims 203-216, wherein the NT-proBNP is greater than 125 pg/mL.~~

~~223. The method of claim 222 wherein NT-proBNP is greater than 300 pg/mL.~~

~~224. The method of any one of claims 203-223, wherein the subject is suffering from a symptom of a cardiovascular disease.~~

~~225. The method of claim 224, wherein the symptom comprises shortness of breath, dizziness, chest pain, syncope, or a limit on an activity of daily living.~~

~~226. The method of claim 225, wherein the limit on an activity of daily living is selected from the group consisting of a limit on personal care, mobility, or eating.~~

~~227. The method of any one of claims 203-226, wherein the subject experiences a reduction in the risk of a major cardiovascular event selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~228. The method of any one of claims 203-224, wherein the treatment further comprises measuring the level in the subject of (a) cardiac troponin, and/or an (b) NT-proBNP or BNP, and/or (c) E/e'.~~

~~229. The method of claim 228, wherein cardiac troponin is cardiac troponin T (cTnT), high sensitivity cTnT (hs-cTnT), cardiac troponin I (cTnI), or high sensitivity cTnI (hs-cTnI).~~

~~230. The method of claims of any preceding claims, wherein the measurements are conducted by echocardiogram (ECHO), magnetic resonance imaging (MRI), computed tomography (CT) scan, or cardia catheter.~~

~~231 The method of any one of claims 203-230, wherein the treatment further comprises assessing a NYHA classification score of the subject before and after administration of the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof, wherein a decreased NYHA score after administration of mavacamten or a pharmaceutically acceptable salt thereof indicates a reduction in the extent of the disease in the subject.~~

232. The method of claim 231, further comprising the step of administering the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt until the subject has moved from a Class III to Class II, or Class II to Class I NYHA classification.

233. The method of any one of claims 203-232, wherein the treatment further comprises determining a KCCQ score of the subject before and after administration of the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof, wherein an increased KCCQ score after administration of the myosin inhibitor indicates a reduction in the extent of the disease in the subject.

234. The method of any one of claims 203-233, wherein the treatment further comprises assessing peak oxygen consumption (VO_2) and/or VE/VCO_2 slope in the subject during exercise before and after administration of the therapeutically effective amount of a mavacamten or a pharmaceutically acceptable salt thereof, wherein the peak oxygen consumption (VO_2) in the subject increases.

235. The method of any one of claims 203-234, wherein the subject experiences a reduction in the risk of a major cardiovascular event, wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.

236. The method of claim 235, wherein the subject experiences a statistically significant reduction in their level(s) of (a) cardiac troponin and/or (b) NT-proBNP or BNP.

237. A method for treating a disease in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a myosin inhibitor, wherein the subject has a LVEF of greater than 50%, and one or more of: (a) an elevated level of cardiac troponin or (b) an elevated level of NT-proBNP or BNP.

~~238. The method of claim 237, wherein the subject has preserved systolic function or normal or systolic hyper-contractility.~~

~~239. The method of claim 238, wherein subject has an LVEF greater than or equal to 55%.~~

~~240. The method of claim 238, wherein the subject has a global longitudinal strain (GLS) less than or equal to -15.~~

~~241. The method of claim 238, wherein the subject has an s' of from about 8.1 to about 9.5.~~

~~242. The method of claim 238, wherein the subject has left ventricular fractional shortening (LVFS) of greater than or equal to 25.~~

~~243. The method of claim 237, wherein the subject has LVOT greater than 40 mmHg.~~

~~244. The method of claim 237, wherein the subject has diastolic dysfunction.~~

~~245. The method of claim 244, wherein the subject has E/A below the lower limit of normal and/or septal e', lateral e' or average e' below the lower limit of normal~~

~~246. The method of claim 237, wherein the subject has elevated LV filling pressure.~~

~~247. The method of claim 246, wherein the subject has NT-proBNP greater than 125 pg/ml or BNP greater than 100 pg/ml.~~

~~248. The method of claim 246, wherein the subject has E/e' greater than 10.~~

~~249. The method of claim 246, wherein treating the disease with the myosin inhibitor results in the subject experiencing a reduction in left ventricle filling pressures.~~

~~250. The method of claim 249, wherein the reduction is characterized by an improvement in the average E/e'.~~

~~251. The method of claim 237, wherein the subject has left ventricular hypertrophy.~~

~~252. The method of claim 251, wherein the subject has left ventricle wall hypertrophy.~~

~~253. The method of claim 251 or 252, wherein the subject has a left ventricular end-diastolic volume (LVEDV) below the lower limit of normal, or below about 40-45.~~

~~254. The method of claim 251 or 252, wherein the subject has IVS and/or LV posterior WT greater than 10 mm, maximal wall thickness greater than 1.2 mm, or LVMI, LVM, or septal thickness outside the normal range.~~

~~255. The method of any one of claims 251-254, wherein treating the disease with the myosin inhibitor results in the subject experiencing a reduction left ventricular mass, left ventricular wall thickness, interventricular septal thickness, or left ventricular septal thickness.~~

~~256. The method of claim 237, wherein the subject has left atrial enlargement.~~

~~257. The method of claim 256, wherein the subject has a left atrial volume greater than the upper limit of normal.~~

~~258. The method of claim 237, wherein the subject has myocardial injury and/or fibrosis.~~

~~259. The method of claim 258, wherein the subject has elevated levels of cardiac troponin.~~

~~260. The method of claim 258, wherein the subject has late gadolinium enhancement consistent with myocardial injury and/or fibrosis.~~

~~261. The method of claim 258, wherein the subject has T1 mapping consistent with myocardial injury and/or fibrosis.~~

~~262. The method of any of claims 237-261, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.~~

~~263. The method of claim 262, wherein the therapeutically effective amount is from about 2.5 mg to about 15 mg.~~

~~264. The method of claim 262, wherein the therapeutically effective amount is from about 2.5 mg to about 5 mg per day.~~

~~265. The method of claim 262, wherein the therapeutically effective amount is from about 5 mg to about 7.5 mg per day.~~

~~266. The method of claim 262, wherein the therapeutically effective amount is from about 7.5 mg to about 15 mg per day.~~

~~267. The method of any one of claims 237-266, wherein the cardiac troponin is cardiac troponin T (cTnT) or high sensitivity cTnT (hs-cTnT).~~

~~268. The method of claim 267, wherein the cardiac troponin is cardiac troponin I (cTnI) or high sensitivity cTnI (hs-cTnI).~~

~~269. The method of any one of claims 237-268, wherein the BNP is greater than 100 pg/mL.~~

~~270. The method of any one of claims 237-268, wherein the NT-proBNP is greater than 125 pg/mL.~~

~~271. The method of claim 270, wherein the NT-proBNP is greater than 300 pg/mL.~~

~~272. The method of any one of claims 237-271, wherein the subject is suffering from a symptom of a cardiovascular disease.~~

~~273. The method of claim 272, wherein the symptom comprises shortness of breath, dizziness, chest pain, syncope, or a limit on an activity of daily living.~~

~~274. The method of claim 273, wherein the limit on an activity of daily living is selected from the group consisting of a limit on personal care, mobility, or eating.~~

~~275. The method of any one of claims 237-274, wherein the subject experiences a reduction in the risk of a major cardiovascular event selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.~~

~~276. The method of any one of claims 237-275, wherein the treatment further comprises measuring the level of (a) cardiac troponin, and/or (b) NT-proBNP or BNP.~~

~~277. The method of any one of claims 237-276, wherein the treatment further comprises assessing a NYHA classification score of the subject before and after administration of the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof, wherein a decreased NYHA score after administration of mavacamten or a pharmaceutically acceptable salt thereof indicates a reduction in the extent of the disease in the subject.~~

~~278. The method of claim 277, further comprising the step of administering the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt until the subject has moved from a Class III to Class II, or Class II to Class I NYHA classification.~~

~~279. The method of any one of claims 237-278, wherein the treatment further comprises determining a KCCQ score of the subject before and after administration of the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof, wherein an increased KCCQ score after administration of the myosin inhibitor indicates a reduction in the extent of the disease in the subject.~~

280. The method of any one of claims 237-279, wherein the treatment further comprises assessing peak oxygen consumption (VO_2) and/or VE/VCO_2 slope in the subject during exercise before and after administration of the therapeutically effective amount of a mavacamten or a pharmaceutically acceptable salt thereof, optionally wherein the peak oxygen consumption (VO_2) in the subject increases.

281. The method of any one of claims 237-280, wherein the subject experiences a reduction in the risk of a major cardiovascular event, wherein the major cardiovascular event is selected from the group consisting of death, hospitalization for worsening of the disease, and myocardial infarction.

282. The method of any one of claims 237-281, wherein the subject experiences a statistically significant reduction in their level(s) of (a) cardiac troponin and/or (b) NT-proBNP or BNP.

283. A method of administering mavacamten or a pharmaceutically acceptable salt thereof to a subject suffering from HFpEF, comprising:

administering a first dose of mavacamten or a pharmaceutically acceptable salt thereof during a first treatment period to the subject having (1) an elevated NT-proBNP level, an elevated cTnT, or an elevated cTnI, and (2) an LVEF greater than or equal to 50;

determining whether the subject responded to mavacamten by observing the levels of change in a biomarker in a blood sample and change in the LVEF of the subject at the end of the first treatment period; and

administering a second dose of mavacamten for a second treatment period if the concentration level of the biomarker in the blood sample decreased and the LVEF has not decreased to below 50.

284. The method of claim 283, wherein the first dose is 2 mg, 2.5 mg or 5 mg per day.

285. The method of claim 283, wherein the second dose is higher in amount per day than the first dose and wherein the second treatment period is longer than the first treatment period.

286. The method of claim 283, wherein the biomarker is selected from the group consisting of cTnT, cTnI, NT-proBNP and BNP.

287. The method of any preceding claim, wherein the myosin modulator or myosin inhibitor is administered as a monotherapy.

288. The method of any one of claims 1-287 or 291-398, wherein the myosin modulator or myosin inhibitor is administered as part of a combination therapy.

289. The method of claim 288, wherein the combination therapy comprises one or more of the following:

a standard of care (SOC) therapy a cardiac condition of the subject or other therapy useful for treating the relevant disease or disorder;

another therapeutic agent such as a beta-blocker, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor antagonist (e.g., an angiotensin II receptor blocker), an angiotensin receptor neprilysin inhibitor (ARNI) (e.g., sacubitril/valsartan), a mineralocorticoid receptor antagonist (e.g., an aldosterone inhibitor such as a potassium-sparing diuretic such as eplerenone, spironolactone, or canrenone), a cholesterol lowering drug (e.g., a statin), a neutral endopeptidase inhibitor (NEPi), a positive inotropic agent (e.g., digoxin, pimobendane, a beta adrenergic receptor agonist such as dobutamine, a phosphodiesterase (PDE)-3 inhibitor such as milrinone, or a calcium-sensitizing agent such as levosimendan), potassium or magnesium, a proprotein convertase subtilisin kexin-type 9 (PCSK9) inhibitor, a vasodilator (e.g., a calcium channel blocker, phosphodiesterase inhibitor, endothelin receptor antagonist, renin inhibitor, or smooth muscle myosin modulator), a diuretic (e.g., furosemide), warfarin, a RAAS inhibitor, an arrhythmia medication, an anticoagulant, an antithrombotic agent, an antiplatelet agent, or any combination thereof;

an ARB selected from A-81988, A-81282, BIBR-363, BIBS39, BIBS-222, BMS-180560, BMS-184698, candesartan, candesartan cilexetil, CGP-38560A, CGP-48369, CGP-49870, CGP-63170, CI-996, CV-11194, DA-2079, DE-3489, DMP-811, DuP-167, DuP-532, E-4177, elisartan, EMD-66397, EMD-73495, eprosartan, EXP-063, EXP-929, EXP-3174, EXP-6155,

~~EXP-6803, EXP-7711, EXP-9270, FK-739, GA-0056, HN-65021, HR-720, ICI D6888, ICI-D7155, ICI-D8731, irbesartan, isoteoline, KRI-1177, KT3-671, KW-3433, losartan, LR-B/057, L-158809, L-158978, L-159282, L-159874, L-161177, L-162154, L-163017, L-159689, L-162234, L-162441, L-163007, LR-B/081, LR-B087, LY-285434, LY-302289, LY-315995, LY-235656, LY-301875, ME-3221, olmesartan, PD-150304, PD-123177, PD-123319, RG-13647, RWJ-38970, RWJ-46458, saralasin acetate, S-8307, S-8308, SC-52458, saprisartan, saralasin, sarmesin, SL-91.0102, tasosartan, telmisartan, UP-269-6, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472,WK-1360, X-6803, valsartan, XH-148, XR-510, YM-358, ZD-6888, ZD-7155, ZD-8731, or zolasartan; and~~

~~an ARNI selected from sacubitril/valsartan (Entresto®) or a sodium-glucose cotransporter 2 inhibitor (SGLT2i) such as empaglifozin (e.g., Jardiance®), dapagliflozin (e.g., Farxiga®), or sotagliflozin.~~

~~290. The method of claim 288, wherein the combination therapy comprises treatment with one or more of an ARNI (e.g., Entresto®), a beta blocker, an MRA, and disopyramide.~~

~~29~~1. Use of a therapeutically effective amount of a myosin modulator in the manufacture of a medicament for ~~A method of~~ treating a subject suffering from oHCM ~~comprising administering a myosin modulator to the subject~~, wherein the subject is eligible for septal reduction therapy (SRT).

~~292. The method of claim 291, wherein the treatment comprises administering a therapeutically effective amount of the myosin modulator to the subject.~~

~~293~~2. The ~~method~~ use of claim ~~292~~1, wherein the treatment lessens the likelihood that the subject will undergo a SRT, lessens the short-term likelihood that the subject will undergo SRT, and/or eliminates the need for the subject to undergo a SRT.

~~294. The method of claim 292, wherein the treatment lessens the short-term likelihood that the subject will undergo SRT.~~

~~295. The method of claim 292, wherein the treatment eliminates the need for the subject to undergo a SRT.~~

~~296~~3. The ~~method~~ use of claim ~~291 or 292~~1, wherein the treatment results in a reduction in interventricular septal (IVS) wall thickness, optionally wherein the treatment reduces the interventricular septal (IVS) wall thickness relative to the IVS thickness prior to receiving the treatment.

~~297. The method of claim 296, wherein the treatment reduces the interventricular septal (IVS) wall thickness relative to the IVS thickness prior to receiving the treatment.~~

~~298~~4. The ~~method~~ use of any one of claims ~~291-297~~1-3, wherein prior to the treatment ~~administration of the myosin modulator~~, the subject had an interventricular septal (IVS) wall thickness to ≥ 13mm and has a family history of HCM and/or the subject had an interventricular septal (IVS) wall thickness to ≥ 15mm.

~~299. The method of claim any one of claims 291-297, wherein prior to the administration of the myosin modulator, the subject had a interventricular septal (IVS) wall thickness to ≥ 15mm.~~

~~300~~5. The ~~method~~ use of any one of claims ~~291-299~~1-4, wherein prior to the treatment, the subject has severe dyspnea or chest pain.

~~301~~6. The ~~method~~ use of any one of claims ~~291-299~~1-4, wherein prior to the treatment, the subject is diagnosed with NYHA Class III or IV, or NYHA Class II with or without exertional symptoms optionally wherein the exertional symptoms are exertion-induced syncope or pre-syncope.

~~302. The method of any one of claims 291-299, wherein the exertional symptoms are exertion-induced syncope or pre-syncope.~~

~~303~~7. The ~~method~~ use of any one of claims ~~291-299~~1-4, wherein prior to the treatment, the subject has a dynamic LVOT gradient at rest or with provocation of ≥ 50 mmHg associated with septal hypertrophy, optionally wherein provocation is determined during a Valsalva maneuver or exercise.

~~304. The method of claim 303, wherein provocation is determined during a Valsalva maneuver or exercise.~~

~~305~~8. The ~~method~~ use of any one of claims ~~291-299~~1-4, wherein prior to the treatment, the subject has a LVEF ≥ 60%.

~~306~~9. The ~~method~~ use of any one of claims ~~291-305~~1-8, wherein the treatment results in an improvement in the NYHA Class and/or an improvement in the KCCQ.

~~307. The method of any one of claims 291-305, wherein the treatment results in an improvement in the KCCQ.~~

~~308~~10. The ~~method~~ use of any one of claims ~~291-307~~1-9, wherein the myosin modulator is a myosin inhibitor.

~~309~~11. The use~~method~~ of claim ~~308~~10, wherein the myosin inhibitor is mavacamten or a pharmaceutically acceptable salt thereof.

~~310~~12. The ~~method~~ use of claim ~~309~~11, wherein the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof is from about 2.5 mg to about 15 mg.

~~311. The method of claim 309, wherein the therapeutically effective amount is from about 5 mg to about 7.5 mg per day, or about 7.5 mg to about 15 mg per day.~~

~~312~~13. The ~~method~~ use of claim ~~309~~11, wherein the initial dose is 5 mg per day for at least four weeks before a dose adjustment.

~~313~~14. The ~~method~~ use of any one of claims ~~309-312~~11-13, wherein the therapeutically effective amount is ~~administered~~ for administration once a day for 16 or more weeks, optionally 32 or more weeks, or optionally 96 or more weeks.

~~314. The method of any one of claims 309-312, wherein the therapeutically effective amount is administered once a day for 32 or more weeks.~~

~~315. The method of any one of claims 309-312, wherein the therapeutically effective amount is administered once a day for 96 or more weeks.~~

~~316~~15. The ~~method~~ use of claim ~~309~~11, wherein the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof is 5 mg per day for 16 or more weeks.

~~317~~16. The ~~method~~ use of claim ~~316~~15, wherein the subject is ~~optionally~~ evaluated for a dose adjustment at week 4, week 8, week 12, or week 16.

~~318. The method of claim 309, wherein the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof is 5 mg per day for 32 or more weeks.~~

~~319. The method of claim 318, wherein the subject is optionally evaluated for a dose adjustment at week 4, week 8, week 12, or week 16, week 20, week 24, week 28, or week 32.~~

~~320. The method of claim 309, wherein the therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof is 5 mg per day for 96 or more weeks.~~

~~321. The method of claim 318, wherein the subject is optionally evaluated for a dose adjustment at week 4, week 8, week 12, or week 16, week 20, week 24, week 28, or week 32, week 44, week 56, week 68, week 80, week 92, week 104, week 116, or week 128.~~

~~322. The method of any one of claims 317, 319, or 321, wherein each dose adjustment comprises reducing the dose to 2.5 mg or 1 mg per day.~~

~~323. The method of any one of claims 317, 319, or 321, wherein each dose adjustment comprises increasing the dose to 7.5 mg or 15 mg per day.~~

~~324~~17. The ~~method~~ use of ~~any one of claims 317, 319, or 321-323~~claim 16, wherein the evaluation for the dose adjustment comprises the assessments of one or more of any of: vital signs (such as temperature, heart rate (HR), respiratory rate, or blood pressure), body weight, NYHA functional classes, adverse events, concomitant medications, physical examination, KCCQ, resting Valsalva, transthoracic echocardiography, transthoracic echocardiogram, postexercise, Accelerometer, Holter monitor application, Single 12-lead ECG, PK sample, blood chemistry and coagulation, a cardiac biomarker, or an exploratory biomarker.

18~~325~~. The ~~method~~ use of claim ~~324~~17, wherein the evaluation comprises assessments of one or more cardiac biomarkers, wherein the one or more cardiac biomarkers comprise NT-proBNP or BNP or cardiac troponin, optionally wherein the cardiac troponin is cardiac troponin I (cTnI), high sensitivity cTnI (hs-cTnI), cardiac troponin T (cTnT) or high sensitivity cTnT (hs-cTnT).

~~326. The method of claim 325, wherein the one or more cardiac biomarkers comprise NT-proBNP or BNP.~~

~~327. The method of claim 325, wherein the one or more cardiac biomarkers comprise cardiac troponin.~~

~~328. The method of claim 327, wherein the cardiac troponin is cardiac troponin I (cTnI) or high sensitivity cTnI (hs-cTnI).~~

~~329. The method of claim 327, wherein the cardiac troponin is cardiac troponin T (cTnT) or high sensitivity cTnT (hs-cTnT).~~

~~330. The method of claim 324, wherein the vital signs comprises temperature, heart rate (HR), respiratory rate, or blood pressure.~~

~~331~~19. The ~~method~~ use of claim ~~324~~17, wherein the evaluation comprises analysis of LVOT gradient, left ventricular ejection fraction (LVEF), left ventricular (LV) filling pressures, or left atrium size in the subject.

~~332~~20. The ~~method~~ use of claim 17~~324~~, wherein the evaluation comprises one or more of:

(a) assessments of changes from the baseline to week 16 in the subject who ~~is~~ has been treated with mavacamten compared with the subject who has been~~is~~ treated with placebo;

(b) assessments of changes from baseline to week 16 compared with changes from baseline to week 32 in the subject who has been~~is~~ treated with mavacamten; and

(c) assessments of changes from the baseline to week 32 in the subject who has been~~is~~ treated with mavacamten compared with the subject who has been~~is~~ treated with placebo from week 1 to week 16 and then has been~~is~~ treated with mavacamten from week 17 to week 32.

~~333. The method of claim 324, wherein the evaluation comprises assessments of changes from baseline to week 16 compared with changes from baseline to week 32 in the subject who is treated with mavacamten.~~

~~334. The method of claim 324, wherein the evaluation comprises assessments of changes from the baseline to week 32 in the subject who is treated with mavacamten compared with the subject who is treated with placebo from week 1 to week 16 and then is treated with mavacamten from week 17 to week 32.~~

~~335~~21. The ~~method~~ use of ~~any one of claims 331 to 334~~claim 19 or 20, wherein the evaluation is to assess changes in NYHA functional classes, in KCCQ-23 scores, in NT-proBNP or BNP levels, in a cardiac troponin cTnI or cTnT, or the LVOT gradient in the subject.

~~336. The method of claim 335, wherein the evaluation is to assess NT-proBNP.~~

~~337. The method of claim 335, wherein the cardiac troponin is cardiac troponin I (cTnI) or high sensitivity cTnI (hs-cTnI).~~

~~338. The method of claim 335, wherein the cardiac troponin is cardiac troponin T (cTnT), or high sensitivity cTnT (hs-cTnT).~~

~~339~~22. The ~~method~~ use of any preceding claims, wherein the subject is reevaluated at week 16, week 32, week 80, and/or week 128 for SRT eligibility.

~~340~~23. The ~~method~~ use of any one of claims ~~324-339~~17-22, wherein the evaluation shows the method of any one of claims ~~291-323~~1-16 lessens or eliminates the need of a SRT for the subject.

~~341. The method of any one of claims 324-339, wherein the evaluation shows the method of any one of claims 291-323 eliminates the need of a SRT for the subject.~~

~~342~~24. The ~~method~~ use of any preceding claim, wherein the subject is eligible for SRT consistent with ACC/AHA 2011 and/or ESC2014 guidelines.

~~343~~25. The ~~method~~ use of any preceding claim, wherein the subject is characterized by one or more of (a)-(c):

(a) NYHA Class III or IV or Class II with or without exertional symptoms;

(b) dynamic LVOT gradient at rest or with provocation (i.e., Valsalva or exercise) ≥ 50 mmHg associated with septal hypertrophy; and

(c) targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

~~344. The method of 343, wherein the subject is characterized by two or more of (a)-(c).~~

~~345. The method of 343, wherein the subject is characterized by all three of (a)-(c).~~

~~346~~26. The ~~method~~ use of any preceding claim, wherein the subject has an elevated troponin level and/or an elevated NT-proBNP or BNP level, optionally wherein the subject has an E/e' >14.

~~347. The method of claim 346, wherein the subject has an E/e' >14.~~

~~348~~27. The ~~method~~ use of any one of claims ~~291-347~~1-26, wherein the subject is refractory to standard of care treatment for oHCM such as treatment with a beta blocker, a calcium channel blocker, disopyramide or any combination thereof.

~~349. The method of any one of claims 291-347, wherein the subject is refractory to treatment of oHCM with a beta blocker, a calcium channel blocker, disopyramide or any combination thereof.~~

~~350~~28. The ~~method~~ use of any one of claims ~~291-349~~1-27, wherein, prior to treatment with a myosin inhibitor, mavacamten or a pharmaceutically acceptable salt thereof, the subject reached their maximum tolerated medical treatment with standard of care oHCM therapy (such as beta blockers, calcium channel blockers, and/or disopyramide) and remained symptomatic NYHA class III or IV with an LVOT gradient greater than or equal to 50 mmHg.

~~351. The method of any one of claims 291-349, wherein, prior to treatment with a myosin inhibitor, or mavacamten or a pharmaceutically acceptable salt thereof, the subject reached their maximum tolerated medical treatment with beta blockers, calcium channel blockers, and/or disopyramide and remained symptomatic NYHA class III or IV with an LVOT gradient greater than or equal to 50 mmHg.~~

~~352~~29. The ~~method~~ use of any one of claims ~~291-351~~1-28, wherein the subject receives adjunctive therapy comprising standard of care treatment, such as a beta blocker, a calcium channel blocker, disopyramide, or any combination thereof, for oHCM during the course of treatment with the myosin inhibitor, or mavacamten or pharmaceutically acceptable salt thereof.

~~353. The method of any one of claims 291-351, wherein the subject receives adjunctive therapy comprising a beta blocker, a calcium channel blocker, disopyramide, or any combination thereof during the course of treatment with the myosin inhibitor, or mavacamten or pharmaceutically acceptable salt thereof.~~

~~354~~30. The ~~method~~ use of any one of claims ~~291-353~~1-29, wherein the subject is classified as NYHA class IV.

~~355. The method of any one of claims 291-354, wherein the oHCM is symptomatic oHCM.~~

~~356~~31. The ~~method~~ use of claim ~~324~~17, wherein the evaluation comprises analysis of LVOT gradient and/or LVEF.

~~357~~32. The ~~method~~ use of claim ~~356~~31, ~~comprising increasing~~wherein the dose of mavacamten is increased if the LVOT gradient in the subject is greater than 30 mmHg and the LVEF in the subject is greater than or equal to 50%.

~~358. The method of any one of claims 291-357, wherein the patient to be treated satisfies the inclusion criteria and exclusion criteria of Example 6.~~

~~359~~33. The ~~method~~ use of claim 2~~93~~, wherein lessening the likelihood that a subject will undergo SRT comprises (1) a reduction in the desire of a patient to proceed with SRT, and/or (2) a resultant change in SRT guideline eligibility such that the patient is ~~is~~ no longer eligible to receive SRT.

~~360~~34. The use of claim 2 or 33~~method any one of claims 293, 294, or 359~~, wherein the change in likelihood is based on an assessment of likelihood at baseline compared to an assessment of likelihood at Week 16 and/or Week 32, and wherein the reduction from baseline of the likelihood that a subject will undergo SRT is achieved by Week 16 and maintained at Week 32.~~.~~

~~361. The method of any preceding claim, wherein the myosin modulator or myosin inhibitor is mavacamten, and mavacamten in crystalline Form A of mavacamten.~~

~~362. A method of treating or alleviating shortness of breath in a patient diagnosed with symptomatic, obstructive HCM, the method comprising administering to the patient a therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof once per day for greater than twenty-one weeks.~~

~~363. The method of claim 362, wherein shortness of breath is measured by a patient-reported questionnaire.~~

~~364. The method of claim 363, wherein the questionnaire comprises two or more questions regarding shortness of breath symptoms of the patient.~~

~~365. The method of claim 364, wherein the questionnaire is HCMSQ-SoB.~~

~~366. The method of any one of claims 362-365, wherein the therapeutically effective amount is from about 2.5 mg to about 15 mg per day.~~

~~367. The method of any one of claims 362-366, wherein mavacamten is administered for at least thirty weeks.~~

~~368. The method of any of claims 362-367, wherein the patient has an LVEF >50%.~~

~~369. The method of any one of claims 362-368, wherein the therapeutically effective amount results in a trough blood plasma concentration of mavacamten in the patient of from about 350 to about 700 ng/mL.~~

~~370. The method of any one of claims 362-369, wherein the therapeutically effective amount results in a post exercise LVOT gradient in the patient of less than about 50 mmHg or less than about 30 mmHg.~~

~~371. A method of increasing the quality of life of a patient diagnosed with symptomatic, obstructive HCM, the method comprising administering to the patient a therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof for at least thirty weeks, wherein the improvement in the quality of life of the patient is measured by an improvement of at least six points in the patient's KCCQ score relative to before treatment with mavacamten or a pharmaceutically acceptable salt thereof.~~

~~372. The method of claim 371, wherein the KCCQ score is based on using any one or all of KCCQ-CSS, KCCQ-OSS, or KCCQ-TSS.~~

~~373. The method of claim 371 or 372, wherein improvement in quality of life is additionally measured by an improvement in shortness of breath.~~

~~374. The method of claim 373, wherein improvement in shortness of breath is determined by a questionnaire comprising two or more questions.~~

~~375. The method of claim 373, wherein improvement in shortness of breath is determined by HCMSQ-SoB score.~~

~~376. The method of claim 371, wherein the patient achieves an improvement of six points in KCCQ score.~~

~~377. The method of any one of claims 371-376, wherein the therapeutically effective amount is from about 2.5 mg to about 15 mg per day.~~

~~378. The method of any of claims 371-377, wherein the patient has an LVEF>50%.~~

~~379. The method of any one of claims 371-378, wherein the therapeutically effective amount results in a trough blood plasma concentration of mavacamten in the patient of from about 350 to about 700 ng/mL.~~

~~380. The method of any one of claims 371-379, wherein the therapeutically effective amount results in a post exercise LVOT gradient in the patient of less than about 30 mmHg or less than about 50 mmHg.~~

~~381. A method of treating symptomatic obstructive HCM in a patient in need thereof comprising:~~

~~administering to the patient mavacamten or a pharmaceutically acceptable salt thereof at a starting dose of from about 2.5 to about 5 mg per day; and~~

~~titrating the starting dose to a second dose of from about 2.5 to about 15 mg per day;~~

~~wherein the patient achieves one or more of the following:~~

~~an improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO2) and a reduction of one or more class in NYHA Functional Classification;~~

~~an improvement of 3.0 mL/kg/min or more in pVO2 with no worsening in NYHA Functional Class;~~

~~an improvement in post-exercise LVOT peak LVOT gradient;~~

~~at least 1 class improvement in NYHA functional class;~~

~~an improvement in pVO2;~~

~~an improvement in KCCQ score;~~

~~an improvement in HCMSQ score;~~

~~a post-exercise LVOT peak LVOT gradient < 50 mmHg;~~

~~a post-exercise LVOT peak LVOT gradient < 30 mmHg;~~

~~an improvement in NT-proBNP levels; and~~

~~an improvement in hs-cTnI levels.~~

~~382. The method of 381, wherein the patient achieves one or more of the following:~~

~~an improvement in EuroQol five-dimensions 5-level questionnaire score;~~

~~an improvement in the Work Productivity and Activity Impairment questionnaire score;~~

~~an improvement in the Patient Global Impression of Change and Patient Global Impression of Severity scores; and~~

an improvement in daily step count and other accelerometer parameters.

383. The method of 381 or 382, comprising titrating the starting dose to achieve a trough blood plasma concentration of mavacamten in the patient of from about 350 to about 700 ng/mL.

384. The method of claim 383, comprising titrating the starting dose to achieve a trough blood plasma concentration of mavacamten in the patient of from about 350 to about 700 ng/mL and a Valsalva LVOT gradient in the patient of less than about 30 mmHg.

385. The method of any one of claims 381-384, wherein the starting dose is 2.5 or 5 mg per day.

386. The method of any one of claims 381-385, wherein the second dose is 2.5, 5, 10, or 15 mg per day.

387. The method of any one of claims 381-386, wherein mavacamten is administered daily for at least about 30 weeks.

388. The method of any one of claims 381-387, wherein the patient to be treated has (a) an oHCM classified as NYHA II or NYHA III, (b) an LVOT peak gradient > 50 mmHG as assessed by echocardiography at rest, after Valsalva maneuver, or post-exercise, and (c) an LVEF > 55%.

389. The method of any one of claims 381-388, wherein the patient satisfies the inclusion and/or exclusion criteria listed in Table 7.0 of Example 7.

390. The method of any one of claims 381-388, wherein titrating the starting dose to a second dose of from about 2.5 to about 15 mg per day comprises titrating the starting dose to a second dose of 2.5 mg per day if Valsalva LVOT gradient in the patient is less than 20 mmHg.

391. A method of treating symptomatic obstructive HCM in a patient in need thereof comprising:

~~administering to the patient mavacamten or a pharmaceutically acceptable salt thereof at a starting dose of from about 2.5 to about 5 mg per day;~~

~~titrating the starting dose to a second dose of from about 2.5 to about 15 mg per day to achieve a Valsalva LVOT gradient in the patient of less than about 30 mmHg;~~

~~wherein the patient achieves one or more of the following:~~

~~an improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO2) and a reduction of one or more class in NYHA Functional Classification;~~

~~an improvement of 3.0 mL/kg/min or more in pVO2 with no worsening in NYHA Functional Class;~~

~~an improvement in post-exercise LVOT peak LVOT gradient;~~

~~at least 1 class improvement in NYHA functional class;~~

~~an improvement in pVO2;~~

~~an improvement in KCCQ score;~~

~~an improvement in HCMSQ score;~~

~~a post-exercise LVOT peak LVOT gradient < 50 mmHg;~~

~~a post-exercise LVOT peak LVOT gradient < 30 mmHg;~~

~~an improvement in NT-proBNP levels; and~~

~~an improvement in hs-cTnI levels.~~

~~392. The method of claim 391, wherein the patient achieves one or more of the following:~~

~~an improvement in EuroQol five dimensions 5-level questionnaire score;~~

~~an improvement in the Work Productivity and Activity Impairment questionnaire score;~~

~~an improvement in the Patient Global Impression of Change and Patient Global Impression of Severity scores; and~~

~~an improvement in daily step count and other accelerometer parameters.~~

~~393. The method of claim 391 or 392, comprising titrating the starting dose to achieve a Valsalva LVOT gradient in the patient of less than about 30 mmHg and a trough blood plasma concentration of mavacamten in the patient of from about 350 to about 700 ng/mL.~~

~~394. The method of any one of claims 391-393, wherein the starting dose is 2.5 or 5 mg per day.~~

~~395. The method of any one of claims 391-394, wherein the second dose is 2.5, 5, 10 or 15 mg per day.~~

~~396. The method of any one of claims 391-395, wherein mavacamten is administered daily for at least about 30 weeks.~~

~~397. The method of any one of claims 391-396, wherein the patient to be treated satisfies the inclusion and/or exclusion criteria in Table 7.0 of Example 7.~~

~~398. The method of any preceding claim, wherein mavacamten is crystalline Form A of mavacamten.~~

~~399. The method of any one of claims 391-398, wherein titrating the starting dose to a second dose of from about 2.5 to about 15 mg per day to achieve a Valsalva LVOT gradient in the patient of less than about 30 mmHg comprises comprises titrating the starting dose to a second dose of 2.5 mg per day if Valsalva LVOT gradient in the patient is less than 20 mmHg.~~

~~400. A method of treating HCM in a patient in need thereof comprising the steps of:~~

~~(a) administering to the patient a therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof once per day;~~

~~(b) temporarily discontinuing administration of mavacamten or a pharmaceutically acceptable salt thereof when the ejection fraction in the patient drops below a threshold ejection fraction; and~~

~~(c) resuming administration to the patient of a therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof once per day.~~

~~401. The method of claim 400, wherein the threshold ejection fraction is 50%.~~

402. The method of claim 400 or 401, comprising (b) temporarily discontinuing administration of mavacamten or pharmaceutically acceptable salt thereof for a period of from about 4 to about 6 weeks, or until ejection fraction returns to above 50%, when the ejection fraction in the patient drops below the threshold ejection fraction.

403. The method of any one of claims 400-402, comprising (c) resuming administration of a therapeutically effective amount of mavacamten or a pharmaceutically acceptable salt thereof to the patient once per day for at least about 4 weeks.

404. The method of any one of claims 400-403, wherein the therapeutically effective amount is from about 2.5 mg to about 15 mg per day.

405. The method of any one of claims 399-403, wherein the therapeutically effective amount results in a trough blood plasma concentration of mavacamten in the patient of from about 350 to about 700 ng/mL,

and/or

the therapeutically effective amount results in a post-exercise LVOT gradient in the patient of less than about 50 mmHg or less than about 30 mmHg.

406. The method of any one of claims 400-405, wherein, subsequent to resuming administration according to step (c), the patient achieves one or more of the following:

an improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO2) and a reduction of one or more class in NYHA Functional Classification;

an improvement of 3.0 mL/kg/min or more in pVO2 with no worsening in NYHA Functional Class;

an improvement in post-exercise LVOT peak LVOT gradient;

at least 1 class improvement in NYHA functional class;

an improvement in pVO2;

an improvement in KCCQ score;

an improvement in HCMSQ score;

a post-exercise LVOT peak LVOT gradient < 50 mmHg;

~~a post-exercise LVOT peak LVOT gradient < 30 mmHg;~~

~~an improvement in NT-proBNP levels; and~~

~~an improvement in hs-cTnI levels.~~

~~406. The method of 405, wherein the patient achieves one or more of the following:~~

~~an improvement in EuroQol five dimensions 5-level questionnaire score;~~

~~an improvement in the Work Productivity and Activity Impairment questionnaire score;~~

~~an improvement in the Patient Global Impression of Change and Patient Global Impression of Severity scores; and~~

~~an improvement in daily step count and other accelerometer parameters.~~

~~407. The method of any of claims 362-406, wherein the patient achieves an improvement in post-exercise peak LVOT gradient and at least 1 class improvement in NYHA functional class.~~

~~408. The method of claim 407, wherein the patient achieves a post-exercise peak LVOT gradient of < 50 mmHg and at least 1 class improvement in NYHA functional class.~~

~~409. The method of claim 408, wherein the patient achieves a post-exercise peak LVOT gradient of < 30 mmHg and at least 1 class improvement in NYHA functional class.~~

~~410. A method of treating hypertrophic cardiomyopathy (HCM) in a subject who is a poor metabolizer of mavacamten, comprising: administering to the subject a starting dose of mavacamten in an amount of 2.5 mg per day, and titrating to a subsequent dose based on pharmacokinetic measurements and/or LVOT gradient in the subject.~~

~~411. The method of claim 410, wherein the subsequent dose is based on a blood plasma concentration of mavacamten in the subject.~~

~~412. The method of claim 410, wherein the subsequent dose is based on the body weight of the subject.~~

~~413. The method of claim 410, wherein the subsequent dose is based on a blood plasma concentration of mavacamten in the subject and the body weight of the subject.~~

~~414. The method of any one of claims 410-413, wherein the subsequent dose is 1 mg.~~

~~415. The method of any one of claims410-413, wherein the subsequent dose is about 5 mg, 10 mg, or 15 mg.~~

~~416. The method of any one of claims 410-415, wherein the poor metabolizer of mavacamten has a CYP2C19 poor metabolizer genotype.~~

~~417. The method of claim 416, wherein the poor metabolizer of mavacamten has a CYP2C19 *2/*2, *2/*3, or *3/*3 genotype.~~

~~418. The method of any one of claims 410-417, wherein the poor metabolizer of mavacamten is an Asian descendant.~~

~~419. The method of claim 418, wherein the poor metabolizer of mavacamten is a Japanese descendant.~~

~~420. The method of any one of claims 410-419, wherein administration of the subsequent dose maintains the blood plasma concentration of mavacamten in the subject between 350 and 700 ng/mL.~~

~~421. The method of any one of claims 410-419, wherein the subsequent dose is about 1 mg if the blood plasma concentration of mavacamten in the subject after administration of the starting dose is over 700 ng/mL.~~

~~422. The method of any one of claims 410-419, wherein the subsequent dose is about 5 mg if the blood plasma concentration of mavacamten in the subject after administration of the starting~~

~~dose is below 350 ng/mL and the Valsalva gradient of the subject after administration of the starting dose is greater than or equal to 30 mmHg.~~

~~423. The method of any one of claims 410-422, wherein the HCM is obstructive HCM (oHCM).~~

~~424. The method of any one of claims 410-423, wherein the method reduces the risk of adverse events in the subject who is a poor metabolizer of mavacamten.~~

~~425. The method of any one of claims 410-424, wherein the method reduces the risk of systolic dysfunction in the subject who is a poor metabolizer of mavacamten.~~

~~426. A method of treating HCM in subject who is an Asian descendant, comprising:~~

~~administering to the subject a starting dose of mavacamten in an amount of 2.5 mg per day, and titrating to a subsequent dose based on pharmacokinetic measurements and/or LVOT gradient of the subject.~~

~~427. The method of claim 426, wherein the subsequent dose is based on a blood plasma concentration of mavacamten in the subject.~~

~~428. The method of claim 426, wherein the subsequent dose is based on the body weight of the subject.~~

~~429. The method of claim 426, where the subsequent dose is based on a blood plasma concentration of mavacamten in the subject and the body weight of the subject.~~

~~430. The method of any one of claims 426-429, wherein the subsequent dose is 1 mg.~~

~~431. The method of any one of claims 426-429, wherein the subsequent dose is 5 mg, 10 mg, or 15 mg.~~

~~432. The method of any one of claims 426-431, wherein administration of the subsequent dose maintains the blood plasma concentration of mavacamten in the subject between 350 and 700 ng/mL.~~

~~433. The method of any one of claims 426-432, wherein the subsequent dose is about 1 mg if the subject weighs below 50 kg or below 45 kg.~~

~~434. The method of any one of claims 426-433, wherein the subsequent dose is about 5 mg if the subject weighs over 70 kg.~~

~~435. The method of any one of claims 426-434, wherein the HCM is obstructive HCM (oHCM).~~

~~436. The method of any one of claims 426-435, wherein the Asian descendant is a Japanese descendant.~~

~~437. The method of any one of claims 426-435, wherein the Asian descendant is a Japanese descendent, a Chinese descendent, a Thai descendent, a Korean descendent, a Filipino descendent, an Indonesian descendent, or a Vietnamese descendent.~~

~~438. The method of any claim herein, wherein the myosin modulator, myosin inhibitor, or mavacamten is crystalline Form A of mavacamten.~~

~~439. The method of claim 438, wherein the crystalline Form A of mavacamten is a purified crystalline form.~~

~~440. A method of treating symptomatic oHCM in a patient in need thereof, comprising:~~

~~administering to the patient a starting dose of 5 mg per day of mavacamten or a pharmaceutically acceptable salt thereof for at least 4 weeks;~~

assessing the patient for LVOT gradient with Valsalva maneuver to determine a first Valsalva gradient;

reducing the dose of mavacamten or a pharmaceutically acceptable salt thereof to 2.5 mg per day when the first Valsalva gradient is less than 20 mmHg;

continuing administration of mavacamten or a pharmaceutically acceptable salt thereof;

assessing the patient for LVOT gradient with Valsalva maneuver to determine a second Valsalva gradient; and

increasing the dose from 2.5 mg to 5 mg per day or from 5 mg to 10 mg per day when the second Valsalva gradient is greater than 30 mmHg.

441. The method of claim 440, wherein the first Valsalva gradient is measured after about 4-6 weeks of administration.

442. The method of claim 440 or 441, wherein the second Valsalva gradient is measured after about 12 weeks of administration.

443. The method of any one of claims 440-442, further comprising assessing the LVEF of the patient prior to administration, wherein administration of the starting dose is initiated when the LVEF is greater than or equal to 55%.

444. The method of any one of claims 440-442, further comprising assessing the LVEF of the patient during administration, and temporarily discontinuing administration when LVEF of the patient is less than 50%.

445. The method of claim 444, wherein administration is discontinued for 4-6 weeks or until LVEF returns to greater than or equal to 50%.

446. The method of any one of claims 440-445, wherein the dose is increased from 2.5 mg to 5 mg per day or from 5 mg to 10 mg per day when the second Valsalva gradient is greater than 30 mmHg and the patient has a LVEF greater than or equal to 55%.

~~447. The method of any one of claims 440-445, further comprising assessing the patient for LVOT gradient with Valsalva maneuver to determine a third Valsalva gradient and increasing the dose from 2.5 mg to 5 mg per day, from 5 mg to 10 mg per day, or from 10 mg to 15 mg per day, when the third Valsalva gradient is greater than 30 mmHg.~~

~~448. The method of claim 447, wherein the dose is increased from 2.5 mg to 5 mg per day, from 5 mg to 10 mg per day, or from 10 mg to 15 mg per day, when the third Valsalva gradient is greater than 30 mmHg and the patient has a LVEF greater than or equal to 55%.~~