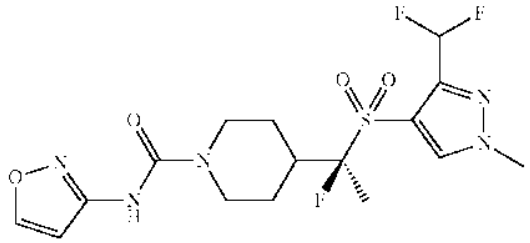
What is claimed is:

1. Use of Compound I in the manufacture of a medicament for~~A method of~~ treating systolic dysfunction in a patient in need thereof, ~~comprising administering to the patient~~wherein Compound I is to be administered orally to the patient at a total daily amount of 25-350 mg, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof.

2. The ~~method~~ use of claim 1, wherein the patient is suffering from a syndrome or disorder selected from the group consisting of heart failure, cardiomyopathy, cardiogenic shock, a condition that benefits from inotropic support after cardiac surgery, myocarditis, atherosclerosis, secondary aldosteronism, myocardial infarction, valve disease, systemic hypertension, pulmonary hypertension or pulmonary arterial hypertension, detrimental vascular remodeling, pulmonary edema, and respiratory failure; and optionally wherein

the heart failure is selected from heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), congestive heart failure, and diastolic heart failure (with diminished systolic reserve),

the cardiomyopathy is selected from ischemic cardiomyopathy, dilated cardiomyopathy, post-infarction cardiomyopathy, viral cardiomyopathy, toxic cardiomyopathy (optionally post-anthracycline anticancer therapy), metabolic cardiomyopathy (optionally cardiomyopathy in conjunction with enzyme replacement therapy), infiltrative cardiomyopathy (optionally amyloidosis), and diabetic cardiomyopathy,

the condition that benefits from inotropic support after cardiac surgery is ventricular dysfunction due to on-bypass cardiovascular surgery,

the myocarditis is viral myocarditis, and/or

the valve disease is mitral regurgitation or aortic stenosis.

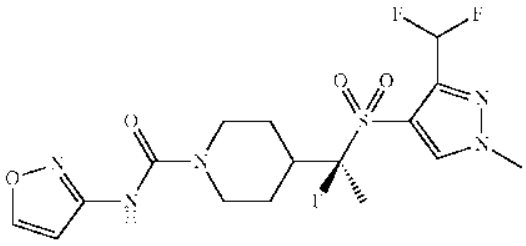
3. The ~~method~~ use of claim 2, wherein said syndrome or disorder is chronic and/or stable.

4. The ~~method~~use of any one of claims 1-3, wherein the patient has heart failure and a diagnosis of any one of NYHA Class II-IV.

5. The ~~method~~ use of any one of claims 1-4, wherein the patient has symptomatic heart failure.

6. The ~~method~~ use of any one of claims 1-5, wherein the patient has acute heart failure.

7. Use of Compound I in the manufacture of a medicament for~~A method of~~ treating heart failure with reduced ejection fraction (HFrEF) in a patient in need thereof, ~~comprising administering to the patient~~wherein Compound I is to be administered orally to the patient at a total daily amount of 10-350 mg, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof.

8. The ~~method~~ use of claim 7, wherein the HFrEF is ischemic HFrEF.

9. The ~~method~~ use of claim 7, wherein the HFrEF is dilated cardiomyopathy (DCM).

10. The ~~method~~ use of claim 9, wherein the patient has a genetic predisposition to DCM or genetic DCM.

11. The ~~method~~ use of claim 10, wherein the genetic DCM is caused by a MYH7 mutation.

12. The ~~method~~ use of any one of claims 1-11, wherein the patient exhibits mitral regurgitation.

13. The ~~method~~ use of any one of claims 1-12, wherein the patient has a left ventricular ejection fraction (LVEF) less than 50%.

14. The ~~method~~ use of claim 13, wherein the patient has an LVEF less than 40%, less than 35%, less than 30%, 15-35%, 15-40%, 15-50%, 20-45%, 40-49%, or 41-49%.

15. The use~~method~~ of any one of claims 1-14, wherein the patient does not have any one or a combination of the following:

a) current angina pectoris;

b) recent (< 90 days) acute coronary syndrome diagnosis;

c) coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) within the prior three months; and

d) uncorrected severe valvular disease.

16. The use~~method~~ of any one of claims 1-15, wherein the treatment results in any one or combination of the following:

a) reduced risk of cardiovascular mortality;

b) reduced risk of cardiovascular-related hospitalization (including, but not limited to, worsening heart failure);

c) improved exercise capacity;

d) improvement in a patient's NYHA classification;

e) delay in clinical worsening; and

f) reduction in severity of cardiovascular-related symptoms.

17. The use~~method~~ of claim 16, wherein the treatment results in an improvement in NYHA classification and an improvement in exercise capacity as measured by pVO_2.

18. The use~~method~~ of claim 16 or 17, wherein the exercise capacity improvement is a >3 mL/kg/min improvement in peak VO_2 (pVO_2).

19. The use~~method~~ of claim 16 or 17, wherein the exercise capacity improvement is a >1.5 mL/kg/min improvement in peak VO_2 (pVO_2).

20. The use~~method~~ of any one of claims 1-19, wherein the patient has an elevated NT-proBNP level.

21. The use~~method~~ according to claim 20, wherein the NT-proBNP level is greater than 400 pg/mL.

22. The use~~method~~ of any one of claims 1-21, wherein the patient is to be administered Compound I at 10-175 mg BID, 25-325 mg QD, or 25-350 mg QD.

23. The use~~method~~ of claim 22, wherein Compound I is to be ingested by the patient with food or within about two hours, within about one hour, or within about 30 minutes of food.

24. The use~~method~~ of any one of claims 1-23, wherein Compound I is to be provided in a solid form with a mean particle size greater than 15 μm in diameter, or between 15 μm and 25 μm in diameter.

25. The use~~method~~ of claim 24, wherein the patient is to be administered a QD dosing greater than 200 mg.

26. The use~~method~~ of any one of claims 1-23, wherein Compound I is to be provided in a solid form with a mean particle size less than 10 μm in diameter.

27. The use~~method~~ of claim 26, wherein the mean particle size of Compound I is between 1 μm and 10 μm in diameter, or between 1 μm and 5 μm in diameter.

28. The use~~method~~ of any one of claims 1-27, wherein the patient

a) is to be administered a Compound I loading dose of 50-250 mg; and

b) continues with a BID or QD maintenance dosing regimen approximately 10-12 hours thereafter, optionally wherein the maintenance dosing regimen is 10-75 mg BID (optionally 10, 25, 50, or 75 mg BID) or 75-125 mg QD.

29. The use~~method~~ of any one of claims 1-27, wherein the patient is to be administered Compound I at 10-75 mg BID, optionally at 10, 25, 50, or 75 mg BID.

30. The use~~method~~ of any one of claims 1-29, wherein the dose results in Compound I plasma concentrations of 1000 to 8000 ng/mL in the patient.

31. The use~~method~~ of claim 30, wherein the dose results in Compound I plasma concentrations of <2000 ng/mL, 1000-4000 ng/mL, 2000-3500 ng/mL, 2000-4000 ng/mL, or >3500 ng/mL.

32. The use~~method~~ of any one of claims 1-31, wherein the patient has right ventricular heart failure.

33. The use~~method~~ of claim 32, wherein the patient has pulmonary hypertension (i.e., pulmonary arterial hypertension).

34. The use~~method~~ of any one of claims 1-33, wherein the patient has left ventricular heart failure.

35. The use~~method~~ of any one of claims 1-34, wherein the ~~administrating~~ administration step is capable of ~~results~~ resulting in improvement of left ventricular function in the patient.

36. The usemethod of claim 35, wherein the improved left ventricular function is improved cardiac contractility as indicated by increased ejection fraction; increased fractional shortening; increased stroke volume; increased cardiac output; improvement in global longitudinal or circumferential strain; and/or decreased left ventricular end-systolic and/or end-diastolic dimensions.

37. The usemethod of any one of claims 1-36, wherein the administrating administration step is capable of resultings in improved functional or exercise capacity of the patient as measured by peak VO_2, reduction in dyspnea, improvement in NYHA Class, improvement in 6-minute walk test, or improvement in activity as determined by accelerometry.

38. The method use of any one of claims 1-37, further comprising administering to the patientwherein an additional medication is to be administered to the patient for improving cardiovascular conditions in the patient.

39. The usemethod of claim 38, wherein the additional medication is a beta blocker, a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), a mineralocorticoid receptor antagonist, an angiotensin receptor-neprilysin inhibitor (ARNI), an sGC activator or modulator, or an antiarrhythmic medication.

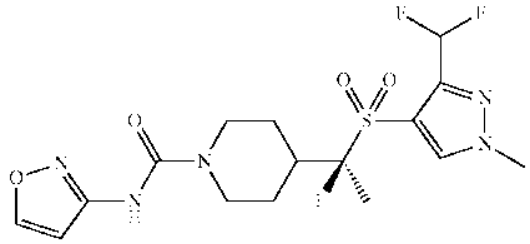
40. The usemethod of claim 39, wherein the additional medication is an ARNI such as sacubitril/valsartan or an SGLT2 inhibitor.

41. The usemethod of any one of claims 1-40, further comprising administering to the patient wherein an analgesic is to be administered to the patient if the patient experiences headache.

42. The usemethod of any one of claims 1-41, further comprising monitoringwherein the patient is to be monitored for NT-proBNP levels, sinus tachycardia, ventricular tachycardia, or palpitation.

43. A kit for use in treating systolic dysfunction in a patient in need thereof, comprising Compound I in the form of tablets or capsules for oral administration, wherein each tablet or capsule comprises 5, 25, 50, 75, or 100 mg of Compound I, and wherein the kit optionally includes a loading dose tablet or capsule,

wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)

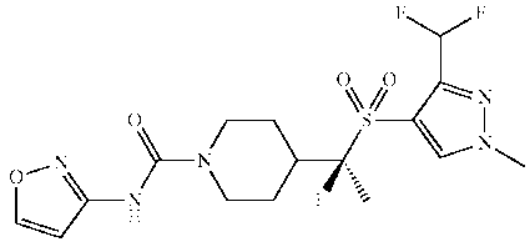


(I),

or a pharmaceutically acceptable salt thereof.

44. A kit for use in treating heart failure with reduced ejection fraction (HFrEF) in a patient in need thereof, comprising Compound I in the form of tablets or capsules for oral administration, wherein each tablet or capsule comprises 5, 25, 50, 75, or 100 mg of Compound I, and wherein the kit optionally includes a loading dose tablet or capsule,

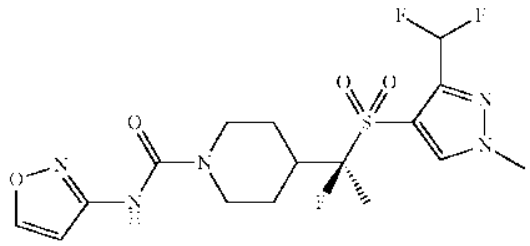
wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof.

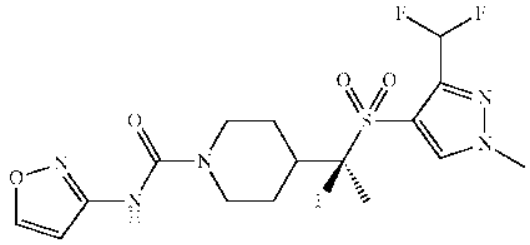
45. Compound I for use in treating systolic dysfunction in a patient in need thereof, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, and wherein Compound I is to be administered orally at a total daily amount of 25-350 mg.

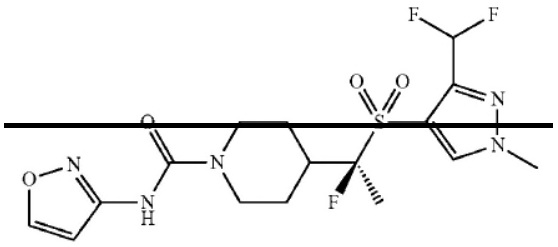
46. Compound I for use in treating heart failure with reduced ejection fraction (HFrEF) in a patient in need thereof, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, and wherein Compound I is to be administered orally at a total daily amount of 25-350 mg.

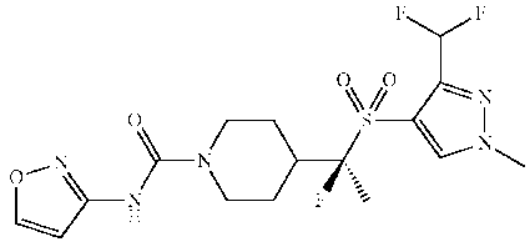
~~47. Use of Compound I for the manufacture of a medicament for treating systolic dysfunction in a patient in need thereof, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)~~



~~(I),~~

~~or a pharmaceutically acceptable salt thereof, and wherein the medicament is for oral administration of Compound I at a total daily amount of 25-350 mg.~~

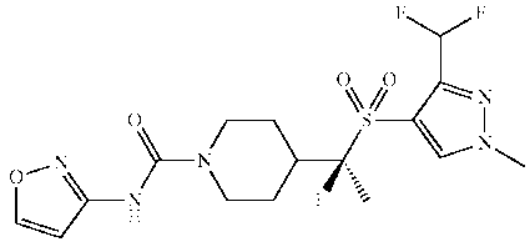
~~48.~~47. Use of Compound I ~~for~~ in the manufacture of a medicament for treating heart failure with reduced ejection fraction (HFrEF) in a patient in need thereof, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, and wherein the medicament is for oral administration of Compound I at a total daily amount of 25-350 mg.

~~49.~~48. A pharmaceutical composition comprising Compound I for use in treating systolic dysfunction in a patient in need thereof, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)

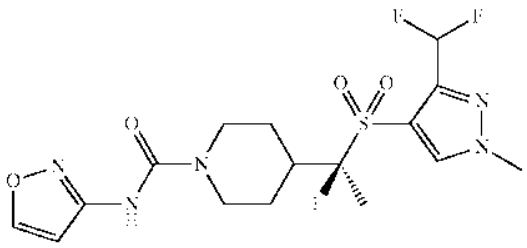


(I),

or a pharmaceutically acceptable salt thereof, and wherein the composition is for oral administration of Compound I at a total daily amount of 25-350 mg.

~~50.~~49. A pharmaceutical composition comprising Compound I for use in treating heart failure with reduced ejection fraction (HFrEF) in a patient in need thereof, wherein Compound I is (R)-

4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)

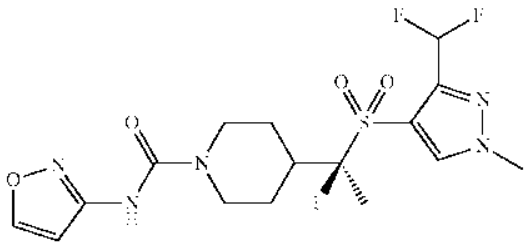


(I),

or a pharmaceutically acceptable salt thereof, and wherein the composition is for oral administration of Compound I at a total daily amount of 25-350 mg.

~~51.~~50. A medicament for use in treating systolic dysfunction in a patient in need thereof, comprising Compound I in the form of tablets or capsules for oral administration, wherein each tablet or capsule comprises 5, 25, 50, 75, or 100 mg of Compound I, and wherein the medicament optionally includes a loading dose tablet or capsule,

wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)

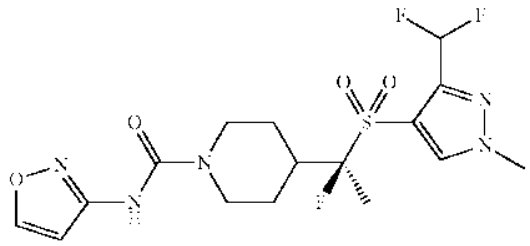


(I),

or a pharmaceutically acceptable salt thereof.

~~52.~~51. A medicament for use in treating heart failure with reduced ejection fraction (HFrEF) in a patient in need thereof, comprising Compound I in the form of tablets or capsules for oral administration, wherein each tablet or capsule comprises 5, 25, 50, 75, or 100 mg of Compound I, and wherein the medicament optionally includes a loading dose tablet or capsule,

wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula



(I), or a pharmaceutically acceptable salt thereof.

~~53.~~52. The kit for use of claim 43 or 44, the Compound I for use of claim 45 or 46, the use of claim 47 ~~or 48~~, the pharmaceutical composition of claim ~~49~~ 48 or ~~50~~49, or the medicament of claim ~~51~~ 50 or ~~52~~51, wherein the treatment is in accordance with the ~~method~~ use of any one of claims 1-42.