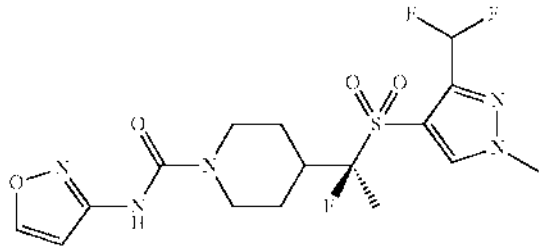
What is claimed is:

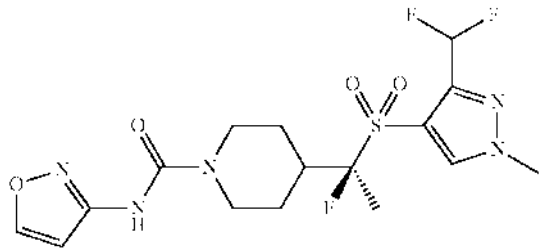
1. Use of Compound I in the manufacture of a medicament for treating atrial dysfunction in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, optionally wherein the patient exhibits atrial fibrillation.

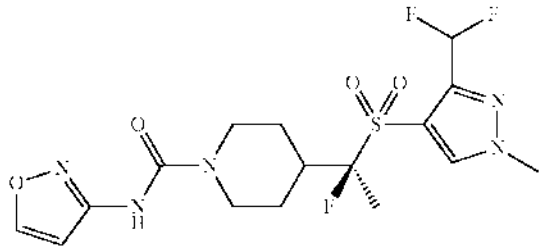
2. Use of Compound I in the manufacture of a medicament for treating atrial cardiomyopathy in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, optionally wherein the patient exhibits atrial fibrillation.

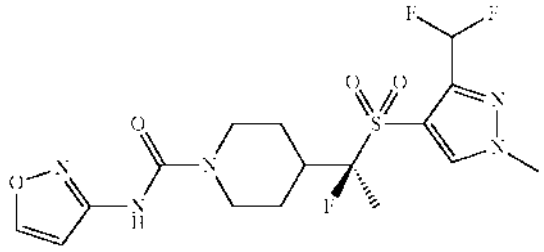
3. Use of Compound I in the manufacture of a medicament for treating atrial tachyarrhythmia in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, optionally wherein the patient exhibits atrial fibrillation.

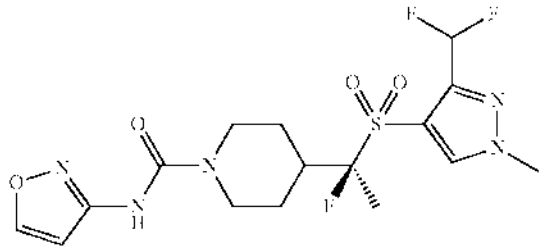
4. Use of Compound I in the manufacture of a medicament for treating atrial fibrillation in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof.

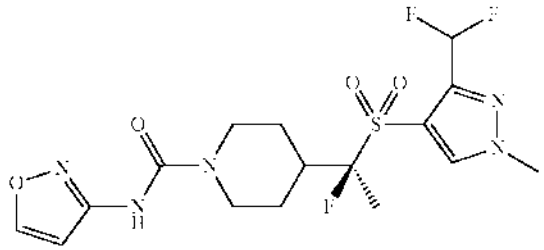
5. Use of Compound I in the manufacture of a medicament for reducing atrial fibrillation recurrence in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, optionally wherein atrial fibrillation recurrence is reduced by 10% or greater.

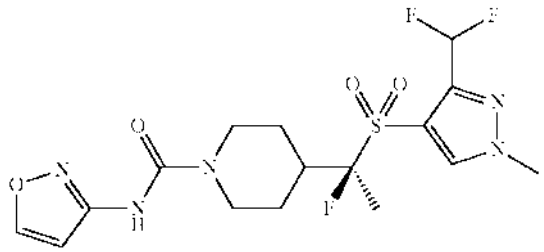
6. Use of Compound I in the manufacture of a medicament for reducing atrial fibrillation burden in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, optionally wherein atrial fibrillation burden is reduced by 10% or greater.

7. Use of Compound I in the manufacture of a medicament for reducing the duration of an atrial fibrillation episode in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, 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)

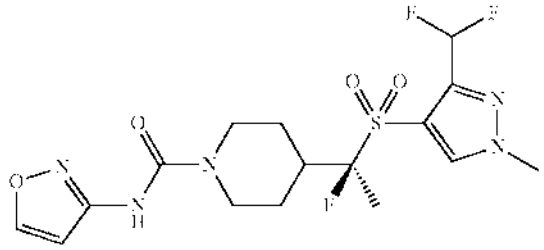


(I),

or a pharmaceutically acceptable salt thereof, optionally wherein the duration of the episode is reduced by 10% or greater.

8. Use of Compound I in the manufacture of a medicament for reducing the number of atrial fibrillation episodes during a monitoring period in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein

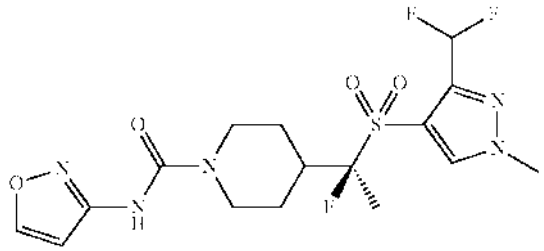
Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, optionally wherein the number of atrial fibrillation episodes is reduced by 10% or greater.

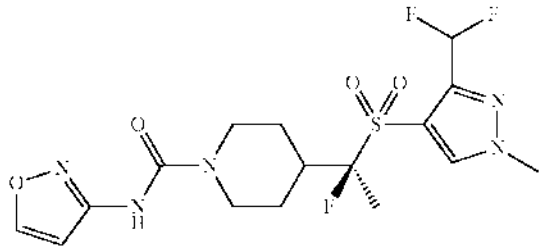
9. Use of Compound I in the manufacture of a medicament for maintaining sinus rhythm in a patient in need thereof, wherein a therapeutically effective amount of Compound I is to be administered to the patient, wherein Compound I is (R)-4-(l-((3-(difluoromethyl)-l-methyl-lH-pyrazol-4-yl)sulfonyl)-l-fluoroethyl)-N-(isoxazol-3-yl)piperidine-l-carboxamide, having the structural formula (I)



(I),

or a pharmaceutically acceptable salt thereof, optionally wherein the patient has sustained atrial tachyarrhythmia for 12 months or less prior to the administering step, further optionally wherein the atrial tachyarrhythmia is atrial fibrillation.

10. Use of Compound I in the manufacture of a medicament for restoring sinus rhythm in a patient exhibiting atrial tachyarrhythmia, wherein a therapeutically effective amount of Compound I is to be administered to the patient in combination with cardioversion, 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, optionally wherein the cardioversion is electrical cardioversion and further optionally wherein the atrial tachyarrhythmia is atrial fibrillation.

11. The use of any one of claims 1-10, wherein the patient also exhibits systolic dysfunction.

12. The use of claim 11, wherein the systolic dysfunction is 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, atrial myopathy, left atrial myopathy, advanced hypertrophic 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.

13. The use of claim 11, wherein the systolic dysfunction is reduced left ventricular ejection fraction (LVEF).

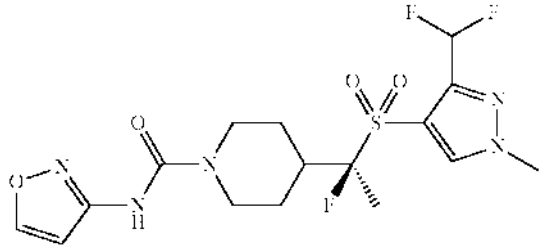
14. The use of any one of claims 1-13, wherein the patient also exhibits diastolic dysfunction.

15. The use of any one of claims 1-14, wherein the patient has heart failure and a diagnosis of any one of NYHA Class II-IV.

16. The use of any one of claims 1-15, wherein the patient has HFrEF.

17. The use of claim 16, wherein the patient exhibits atrial fibrillation; and the therapeutically effective amount of Compound I is capable of alleviating one or more symptoms of HFrEF, maintaining sinus rhythm, reducing atrial fibrillation recurrence, and/or preventing incident atrial fibrillation in the patient.

18. Use of Compound I in the manufacture of a medicament for preventing tachycardia-induced cardiomyopathy in a patient exhibiting atrial fibrillation, wherein a therapeutically effective amount of Compound I is to be administered to the patient, 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, optionally wherein the tachycardia-induced cardiomyopathy is heart failure, optionally heart failure with reduced ejection fraction (HFrEF).

19. The use of any one of claims 1-18 wherein the patient has sustained the tachyarrhythmia or atrial fibrillation for a duration of 12 months or less prior to the administering step.

20. The use of any one of claims 1-19, wherein the atrial fibrillation is paroxysmal or persistent, optionally wherein the atrial fibrillation is persistent and has been sustained for 12 months or less.

21. The use of any one of claims 1-20, wherein the patient has an atrial fibrillation burden of 2-70%.

22. The use of any one of claims 1-21, wherein the patient has postoperative AF.

23. The use of any one of claims 16-22, wherein the patient has a left ventricular ejection fraction (LVEF) of less than 50%, optionally wherein the patient has an LVEF 49% or less, 45% or less, 40% or less, 39% or less, 35% or less, 30% or less, 15-35%, 15-40%, 15-49%, 15-50%, 20-45%, 35-49%, 35-50%, 40-49%, 41-49%, 40-50%, or 41-50%.

24. The use of any one of claims 1-15 and 18-22, wherein the patient has a left ventricular ejection fraction (LVEF) of less than 60%.

25. The use of claim 24, wherein the patient has HFpEF.

26. The use of any one of claims 1-25, wherein the patient has left atrial enlargement.

27. The use of any one of claims 1-26, wherein the patient has atrial myopathy.

28. The use of claim 27, wherein the atrial myopathy is left atrial myopathy.

29. The use of any one of claims 1-28, wherein the patient has previously been treated with ablation or cardioversion.

30. The use of claim 29, wherein the ablation is catheter ablation.

31. The use of claim 29, wherein the cardioversion is electrical cardioversion.

32. The use of any one of claims 1-31, wherein the patient does not have any one or combination of the following:

a) AF burden of <2% or >70%;

b) AF with a reversible etiology;

c) pulmonary hypertension treated with pulmonary vasodilators, wherein the vasodilators are optionally endothelin receptor antagonists or PDE5 inhibitors;

d) known channelopathy, wherein the channelopathy is optionally long QT syndrome, Brugada syndrome, or CPVT;

e) AF diagnosed more than 10 years prior to the start of treatment;

f) long-standing persistent or permanent atrial fibrillation;

g) LA diameter >60 mm;

h) catheter ablation within <6 months prior to the start of treatment, or planned or likely catheter ablation during treatment;

i) introduction of new antiarrhythmic therapy <1 month prior to the start of treatment, or planned introduction of new antiarrhythmic therapy during treatment;

j) electrical cardioversion performed <1 month prior to the start of treatment;

k) heart failure of NYHA Class IV;

l) symptomatic hypotension, or systolic blood pressure <90 mmHg, or diastolic blood pressure >95 mmHg;

m) severe aortic valvular disease or mitral stenosis, planned or anticipated mitral valve repair during treatment, hypertrophic or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease;

n) significant cardiovascular event within $\leq$90 days prior to the start of treatment, wherein the cardiovascular event is optionally acute coronary syndrome or stroke;

o) cardiovascular intervention within $\leq$90 days prior to the start of treatment, wherein the cardiovascular intervention is optionally CABG, PCI, or valvular repair;

p) device implantation within $\leq$45 days prior to the start of treatment, wherein the device is optionally a pacemaker or CRT;

q) hospitalization for heart failure or treatment with IV inotropes within $\leq$90 days prior to the start of treatment;

r) end stage heart failure; or

s) life expectancy <6 months.

33. The use of any one of claims 1-32, wherein the patient is to be administered Compound I at a total daily dose of 10-350 mg.

34. The use of any one of claims 1-32, wherein the patient is to be administered Compound I at 10-175 mg BID, 25-325 mg QD, or 25-350 mg QD.

35. The use of any one of claims 1-32, wherein the patient is to be administered Compound I at 10-75 mg BID, optionally at 10, 25, 50, or 75 mg BID.

36. The use of any one of claims 1-35, wherein the Compound I is to be administered to the patient orally.

37. The use of any one of claims 1-36, wherein Compound 1 is to be administered in a dose resulting in Compound I plasma concentrations of 1000 to 8000 ng/mL in the patient, optionally wherein the dose results in Compound I plasma concentrations of <2000 ng/mL, 2000-3500 ng/mL, or >3500 ng/mL in the patient.

38. The use of any one of claims 1-37, 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.

39. The use of any one of claims 1-38, wherein Compound I is to be provided in a solid form with a mean particle size greater than 15 μm in diameter, less than 10 μm in diameter, between 15 μm and 25 μm in diameter, between 1 μm and 10 μm in diameter, or between 1 μm and 5 μm in diameter.

40. The use of any one of claims 1-39, wherein the patient has undergone an electrical cardioversion before or after the administering step, optionally where the electrical cardioversion is performed no more than 24 hours before or after the administering step.

41. The use of any one of claims 1-40, wherein an additional medication is to be further administered to the patient for improving cardiovascular conditions in the patient, optionally wherein the additional medication is a beta blocker, an anticoagulant, a vitamin K antagonist, a calcium channel 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 SGLT2 inhibitor, an sGC activator or modulator, an antiarrhythmic medication, or any combination thereof.

42. The use of any one of claims 1-40, an anticoagulant and an antiarrhythmic agent are to be further administered to the patient.

43. The use of any one of claims 1-40, an anticoagulant and a rate control agent are to be further administered to the patient, optionally wherein the rate control agent is a beta-blocker, digoxin, or amiodarone.

44. The use of any one of claims 1-40, an anticoagulant; a diuretic; and an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), and/or mineralocorticoid receptor antagonist are to be further administered to the patient.

45. The use of any one of claims 1-44, wherein the use results in any one or combination of the following:

a) reduced risk of urgent outpatient intervention for atrial dysfunction, systolic dysfunction, or both;

b) improved quality of life as measured through 6-MWT or KCCQ;

c) improved exercise capacity;

d) improvement in a patient's NYHA classification;

e) delay in clinical worsening;

f) reduction in severity of cardiovascular-related symptoms;

g) increased left atrial ejection fraction (LAEF);

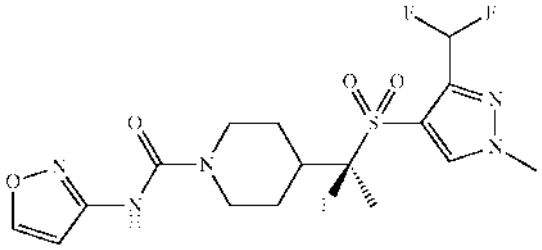
h) decreased left atrial volume ($LA_{min}VI$); and

i) improved left atrial function index (LAFI).

46. The use of any one of claims 1-45, wherein the use results in reduced cardiovascular death or hospitalization.

47. Compound I, or a pharmaceutical composition comprising Compound I and a pharmaceutically acceptable excipient, for use in treating atrial dysfunction, 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).