

CLAIMS

1. A method of treating a patient having a heart failure, comprising:
administering into heart cells of the patient having a classification of congestive heart failure (CHF), at least one total dose of a rAAV vector comprising a nucleic acid sequence encoding a phosphatase inhibitor (I-1) protein that inhibits phosphatase activity,
wherein, at least one dose of the rAAV is selected from a total dose-range of about 10^{13} vg to about 10^{15} vg, and
wherein, at least twelve months post-administration there is an improvement in the classification of congestive heart failure.
2. The method of claim 1, wherein the classification is based upon a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC), Minnesota LIVING WITH HEART FAILURE® Questionnaire (MLHFQ), Kansas City Cardiomyopathy questionnaire (KCCQ), or the 2016 European Society of Cardiology guidelines (ESCG), the Japanese heart failure Society (JHFS) guidelines, The Japanese Circulation Society (JCS) Guidelines, or, the New York Heart Association (NYHA).
3. The method of claim 1 or 2, wherein there is an improvement in the classification of at least one level 12 months after administration of the rAAV.
4. The method of claim 1 or 2, wherein there is an improvement in the classification of at least one level within six months after administration of the rAAV.
5. The method of claim 1, wherein twelve months post-administration there is an improvement of at least 2 levels in the Classification.
6. The method of any of claims 1-5, wherein the classification system is NYHA and the level of classification is selected from the group consisting of: Class I, Class II, Class III, and Class IV.
7. The method of any of claims 1-5, wherein the classification system is the American College of Cardiology/American Heart Association (ACC/AHA) complementary staging system and the level of classification is selected from the group consisting of: Stages A, Stage B, Stage C, Stage D.
8. The method of any of claims 1-5, wherein the classification system is KCCQ and the level of classification is a KQQC overall summary score range selected from the group consisting of: KCCQ fair to excellent scores of 50 to 100, very poor to fair scores of 0 to 49, good to excellent scores of 75 to 100, and very poor to good scores of 0 to 74.
9. A method of treating a patient having cardiomyopathy, comprising:
administering into heart cells of the patient at least one total dose of a rAAV vector comprising a nucleic acid sequence encoding a phosphatase inhibitor (I-1) protein that inhibits phosphatase activity,

wherein, at least one dose of the rAAV is selected from a total dose-range of about 10^{13} vg to about 10^{15} vg, and

wherein, at least twelve months post-administration there is an improvement in the at least one parameter from a baseline level in the patient, where the at least one parameter is selected from the group consisting essentially of:

- a. ejection fraction (EF),
 - b. end systolic volume (ESV)
 - c. cardiac contractility, selected from ejection fraction (EF) and fractional shortening (FS)
 - d. cardiac volumes selected from any of: end diastolic volume (DV) and end systolic volume (ESV),
 - e. functional criteria, selected from any of: a 6-minute walk test (6MWT), exercise and VO₂max;
 - f. BNP level,
 - g. Pro-BNP level
 - h. biomarker level, wherein the biomarker level is selected from the group of: troponin, serum creatinine, cystatin-C, or hepatic transaminases,
 - i. Patient-reported outcomes (PROs), such as reduced symptoms, health-related quality of life (HRQOL), or patient perceived health status, and
 - j. decrease in any of: mortality risk due to heart failure, reduced hospitalization due to heart failure symptoms, or therapeutic intervention for treatment of heart failure.
10. The method of claim 9, wherein there is an improvement of at least 2 parameters at least 12 months after administration.
11. The method of claim 10, wherein there is an improvement of at least 3 parameters at least 12 months after administration.
12. The method of claim 11, wherein there is an improvement of at least 4 parameters at least 12 months after administration.
13. The method of claim 12, wherein there is an improvement of at least 5 parameters at least 12 months after administration.
14. The method of claim 9, wherein the improvement is selected from any of:
- a. at least a 5% or more increase in ejection fraction from baseline,
 - b. at least a 10% decrease, or at least a 20ml decrease in end systolic volume from baseline,
 - c. at least a 50-meter increase in 6-minute walk test from baseline,
 - d. at least a 40% decrease in BNP levels (pg/ml) in the blood from baseline,
 - e. at least a 35% decrease in pro-BNP levels (pg/ml) in the blood from baseline,

- f. at least a 10% reduction in a biomarker selected from: troponin, serum creatinine, cystatin-C, or hepatic transaminases from a baseline level of the same biomarker,
 - g. at least a 1.5ml/kg/min increase in myocardial oxygen consumption (MVO₂) from baseline, or
 - h. a discharge from hospital due to improved HF symptoms, or a reduced intervention selected from a decrease in the use of any of: inotropes, vasodilators, diuretics due to improved HF symptoms in the subject.
15. The method of claim 1 or 14, wherein the rAAV vector further comprises CMV promoter or a synthetic promoter, operatively linked to the phosphatase inhibitor protein.
16. The method of any of claims 1-15, wherein the total dose is administered as any of the following administration methods:
- a. over a period of time of about 20 minutes to about 30 minutes,
 - b. administered in a series of sub-doses, wherein each sub-dose is administered over a period of time of about 1 minute to about 5 minutes,
 - c. administered in a series of five sub-doses, each sub-dose is administered over a period of time of about 1 minute to about 5 minutes, and wherein the five sub-doses are administered over a period of about 20 minutes to about 30 minutes.
17. The method of any of claims 1-16, wherein the rAAV vector comprises a capsid that detargets the liver.
18. The method of any of claims 1-17, wherein the rAAV is selected from the group consisting of AAV1, AAV2, AAV6, AAV8, AAV9, AAV2i8, rA10, AAV2.5 and AAV2G9.
19. The method of any of claims 1-18, wherein the rAAV vector is AAV2i8.
20. The method of any of claim 1-19, wherein at least one total dose of the rAAV is 10^{13} vg, 3×10^{13} vg, 10^{14} vg, 3×10^{14} vg, or, 10^{15} vg.
21. The method of any of claims 1-20, wherein the phosphatase inhibitor (I-1) protein is a constitutively active protein (I-1c).
22. The method of claim 21, wherein the s I-1c is selected from any of:
- a. a polypeptide comprises at least amino acid residues 1-54 of SEQ ID NO: 1, wherein SEQ ID NO: 1 is truncated at the C-terminus at amino acid 70, 67, 66, 65, or 61, or 54, and where there is an aspartic acid at position 35 (T35D),
 - b. a polypeptide comprising amino acids 1-54 of SEQ ID NO: 1 or a functional fragment thereof, wherein the functional fragment has at least 85% sequence identity to amino acid residues 1-54 of SEQ ID NO: 1, or truncated at the C-terminus at amino acid 70, 67, 66, 65, or 61, or 54, and where there is an aspartic acid at position 35 (T35D).
23. The method of any of claims 1-22, wherein the rAAV genome comprises nucleic acid sequence selected from the group consisting of: SEQ ID NO: 413-441.

24. The method of claim 21, wherein the nucleic acid sequence encoding the I-1 polypeptide is selected from
- a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an amino acid that is not T,
 - a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an amino acid selected from any of: aspartic acid (D), glutamic acid (E), asparagine (N), glutamine (Q),
 - a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with aspartic acid (D), or a conservative amino acid of aspartic acid.
25. The method of any of claims 1-24, wherein the nucleic acid sequence encoding the I-1 protein is a codon optimized nucleic acid sequence.
26. The method of any of claims 1-25, wherein the nucleic acid sequence encoding the I-1 protein is selected from any of SEQ ID NO: 385-412, or a nucleic acid sequence having at least 80% sequence identity to SEQ ID NO: 385-412.
27. The method of any of claims 1-26, wherein the subject with cardiomyopathy has non-ischemic heart failure and/or non-ischemic cardiomyopathy.
28. The method of any of claims 1-27, wherein the subject with cardiomyopathy has a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation.
29. The method of claim 29, wherein the subject with a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation has a disease or disorder selected from the group consisting of: Arrhythmogenic right ventricular cardiomyopathy, Atrial myxoma, familial, Atrial septal defect ostium primum, Atrial septal defect sinus venosus, Barth syndrome, muscular dystrophy, Buerger disease, Cardioencephalomyopathy, Chromosome 1p36 deletion syndrome, Congenital generalized lipodystrophy type 4, Congenital heart block, Dilated cardiomyopathy, Duchenne muscular dystrophy (DMD), Fabry disease, Familial atrial fibrillation, Familial dilated cardiomyopathy, Familial hypertrophic cardiomyopathy, Familial progressive cardiac conduction defect, Familial thoracic aortic aneurysm and aortic dissection, Fibromuscular dysplasia, Friedreich ataxia, Gaucher disease, Glycogen storage disease (types 2, 3 or 4), His bundle tachycardia, Hurler syndrome, Hypoplastic left heart syndrome, Infantile histiocytoid cardiomyopathy, Intracranial arteriovenous malformation, Isobutyryl-CoA dehydrogenase deficiency, Kallikrein hypertension, Kawasaki disease, Kearns-Sayre syndrome, Left ventricular noncompaction, Limb-girdle muscular dystrophy (types 1B, 2E, 2F, 2M, 2C, 2D), Limited systemic sclerosis, Long QT syndrome 1, Lymphedema and cerebral arteriovenous anomaly, Lymphocytic vasculitis, Microcephaly-cardiomyopathy; Mitochondrial encephalomyopathy

lactic acidosis and stroke-like episodes, Mitochondrial trifunctional protein deficiency, Myotonic dystrophy type 1, Neonatal stroke, Noonan syndromes 1 -, 2-, 3-, 4-, 5- and 6, Peripartum cardiomyopathy, Peters plus syndrome, PGM1-CDG, PHACE syndrome, Phospholamban Arg 14 Deletion, Postural orthostatic tachycardia syndrome, Primary carnitine deficiency, Progressive familial heart block (types 1A, 1B and 2), Pseudohypoaldosteronism type 2, Pulmonary arterial hypertension, Pulmonary atresia with intact ventricular septum, Pulmonary atresia with ventricular septal defect, Pulmonary valve stenosis, Pulmonary vein stenosis, Pulmonic stenosis, Renoprival hypertension, Retinal arterial macroaneurysm with supraaortic pulmonic stenosis, Right ventricle hypoplasia, Sarcoidosis, Sengers syndrome, Situs inversus, Sudden Arrhythmia Death Syndrome, Supraaortic aortic stenosis, Swyer syndrome, TANGO2-Related Metabolic Encephalopathy and Arrhythmias, TARP syndrome, Tetralogy of Fallot, Timothy syndrome, Tricuspid atresia, Vici syndrome, VLCAD deficiency and Williams syndrome.

30. The method of any of claims 1-29, wherein the subject with cardiomyopathy has an ischemic cardiomyopathy.
31. The method of any of claims 1-30, wherein the subject with cardiomyopathy has heart failure.
32. The method of claim 31, wherein the subject with heart failure has a classification that is equivalent to class III or above in the New York Heart Association (NYHA) classification system.
33. The method of any of claims 30-32, wherein the subject with heart failure has a cardiovascular disease or heart disease is selected from any of: congestive heart failure (CHF), left ventricular remodeling, peripheral arterial occlusive disease (PAOD), dilated cardiomyopathy (DCM) including idiopathic dilated cardiomyopathy (IDCM), coronary artery disease, ischemia, arrhythmia, myocardial infarction (MI), abnormal heart contractility, acute (decompensated) heart failure (AHF), abnormal Ca^{2+} metabolism, myocardial ischemia, atherosclerosis, cardiomyopathy, idiopathic cardiomyopathy, genetic disorder induced cardiomyopathy, cardiac arrhythmias, muscular dystrophy, muscle mass abnormality, muscle degeneration, infective myocarditis, drug- or toxin-induced muscle abnormalities, hypersensitivity myocarditis, an autoimmune endocarditis and congenital heart disease and pulmonary heart hypertension.
34. The method of any of claims 1-33, wherein the subject with cardiomyopathy has reduced ejection fraction (rEF or HFrEF), or, preserved ejection fraction (HFpEF).
35. The method of any of claims 1-34, wherein at least twelve months post-administration of the rAAV there is an improvement of at least one class in a classification of heart failure from a baseline level, wherein the classification of heart failure is assessed by at least one of the following:
 - a. a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC), the 2016 European Society of Cardiology guidelines (ESC), the

- Japanese heart failure Society (JHFS) guidelines, The Japanese Circulation Society (JCS) Guidelines, or, the New York Heart Association (NYHA); or equivalent thereof, or
- b. a health-related quality of life (HRQL) questionnaire selected from the group consisting from any of: Minnesota LIVING WITH HEART FAILURE® Questionnaire (MLHFQ), or Kansas City Cardiomyopathy questionnaire (KCCQ), Chronic Heart Failure Questionnaire (CHFQ), Quality of Life Questionnaire for Severe Heart Failure (QLQ-SHF), Left Ventricular Dysfunction (LVD-36) questionnaire, and the Left Ventricular Disease Questionnaire (LVDQ).
36. The method of claim 35, wherein there is an improvement in the classification of at least one level within six months after administration of the rAAV.
37. The method of claim 35, wherein there is an improvement in the classification of at least two levels within twelve months after administration of the rAAV.
38. The method of claim 35, wherein there is an improvement of at least a 10 point decrease in quality of life MLWHFQ or KCCQ from the baseline level.
39. The method of any of claims 1-38, wherein the subject is administered a vasodilator concurrent with and/or, before, and/or, after the administration of the at least one total dose of a rAAV vector.
40. The method of any of claims 1-39, wherein the subject is administered an immune modulator concurrent with, or before, or after the administration of the at least one total dose of a rAAV vector.
41. A pharmaceutical composition comprising an AAV vector that comprises a codon optimized I-Ic nucleic sequence selected from any of SEQ ID NO: 385-412, or nucleic acid sequence having at least 80% sequence identity to SEQ ID NOS: 385-412.
42. The pharmaceutical composition of claim 41, wherein the codon optimized nucleic acid sequence is operably linked to a CMV promoter or a synthetic promoter.
43. The pharmaceutical composition of claim 41, comprising a nucleic acid sequence selected from the group consisting of: SEQ ID NO: 41-42, or a nucleic acid sequence having at least 80% sequence identity to SEQ ID NOS: 385-412.
44. The pharmaceutical composition of any of claims 41-43, for the use in a method according to any of claims 1-40.
45. An adeno-associated virus (AAV) vector comprising a nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide operably linked to a promoter selected from any of:
a cardiac-specific promoter selected from Table 2A or a variant thereof,
a muscle-specific promoter active in cardiac and skeletal muscle, or a variant thereof, or
any promoter when a cardiac tissue specific enhancer is present.

46. The AAV vector of claim 45, wherein muscle-specific promoter active in cardiac and skeletal muscle is selected from Table 5A or Table 13A or a variant thereof.
47. The AAV vector of any of claims 45-46, wherein the AAV is selected from the group consisting of adeno-associated virus-1 (AAV1), AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9 and AAV2i8.
48. The AAV vector of any of claims 45-47, wherein the AAV comprises a capsid that detargets the liver.
49. The AAV vector of any of claim 45-48, wherein the AAV is AAV2i8.
50. The AAV vector of any of claims 45-49, wherein the phosphatase inhibitor (I-1) polypeptide is a constitutively active protein (I-1c).
51. The AAV vector of any of claims 45-50, wherein the I-1c is selected from any of:
- a polypeptide comprises at least amino acid residues 1-65 of SEQ ID NO: 1 or a functional equivalent thereof;
 - a polypeptide comprising at least amino acids 1-54 of SEQ ID NO: 1, wherein the polypeptide is truncated at a C-terminus at amino acid selected from residue 70, 67, 66, 65, or 61, or 54, and where there is an aspartic acid at position 35 (T35D),
 - a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1 or a functional equivalent thereof having at least 85% sequence identity to amino acid residues 1-65 of SEQ ID NO: 1, or,
 - a polypeptide selected from any of: SEQ ID NOS: 507 or 527-532 or a functional equivalent thereof having at least 85% sequence identity to amino acid residues of any of SEQ ID NOS: 507 or 527-532.
52. The AAV vector of any of claims 45-51, wherein the nucleic acid sequence encoding a I-1 polypeptide is selected from:
- a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an amino acid that is not T,
 - a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an acid amino acid selected from any of: aspartic acid (D), glutamic acid (E), asparagine (N), glutamine (Q),
 - a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with aspartic acid (D), or a conservative amino acid of aspartic acid.
53. The AAV vector of any of claims 45-52, wherein the polypeptide is selected from: amino acids 1-54 of SEQ ID NO: 1, amino acids 1-61 of SEQ ID NO: 1, amino acids 1-65 of SEQ ID NO: 1, amino acids

- 1-66 of SEQ ID NO: 1, amino acids 1-67 of SEQ ID NO: amino acids 1 or 1-77 of SEQ ID NO: 2, or a functional variant thereof, wherein the threonine at position 35 of SEQ ID NO: 1 is replaced with an aspartate acid (T35D), or a conservative amino acid of aspartate.
54. The AAV vector of any of claims 45-50, wherein the nucleic acid sequence encoding the I-1 polypeptide is a codon optimized nucleic acid sequence.
55. The AAV vector of any of claims 45-54, wherein the codon optimized nucleic acid sequence has reduced CpG content or reduced CpG islands as compared to the wild-type reference sequence of a SEQ ID NO: 1, or a fragment thereof.
56. The AAV vector of any of claims 45-54, wherein the nucleic acid sequence encoding the I-1 polypeptide is a codon optimized nucleic acid sequence selected from any of: SEQ ID NO: 385-412 or a nucleic acid sequence at least 80% sequence identity to SEQ ID NO: 385-412
57. The AAV vector of any of claim 45-56, further comprising at least one ITR located 5' of the nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide operably linked to the cardiac-specific promoter or muscle-specific promoter.
58. The AAV vector of any of claim 45-57, further comprising at least two ITRs flanking the nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide operably linked to the cardiac-specific promoter or muscle-specific promoter.
59. The AAV vector of any of claim 45-58, wherein the ITR sequences are selected from any one or more of: SEQ ID NO: 70-78, or a nucleic acid having at least 85% sequence identity to SEQ ID NO: 70-78.
60. The AAV vector of any of claims 45-59, further comprising a reverse poly A sequence or double stranded RNA termination element, wherein the reverse polyA sequence or double stranded termination element are located 3' of the nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide.
61. The AAV vector of claim 60, wherein the reverse poly A sequence, or double stranded RNA termination element is located between 3' of the nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide and 5' of the right ITR.
62. The AAV vector of any of claims 45-61, wherein the nucleic acid sequence can further comprise a nucleic acid sequence encoding at least one immune modulator.
63. The AAV vector of any of claims 45-61, present in a composition or solution, further comprising an immune modulator.
64. The AAV vector of any of claims 45-63, further comprising a polyA sequence selected from any of SV40 polyA (SEQ ID NO: 334), HGH poly A (SEQ ID NO: 66), SEQ ID NO: 284-287, SEQ ID NO

331-335, wherein the polyA sequence is located 3' of the nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide.

65. A pharmaceutical composition comprising:

(i) adeno-associated virus (AAV) vector comprising a nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide operably linked to any one of:

- a. a cardiac-specific promoter selected from Table 2A or a variant thereof,
- b. a muscle-specific promoter active in cardiac and skeletal muscle, or
- c. any promoter when a cardiac tissue specific enhancer is present, or a variant thereof; and

(ii) a pharmaceutically acceptable carrier.

66. The pharmaceutical composition of claim 65, wherein muscle-specific promoter active in cardiac and skeletal muscle is selected from Table 5A or Table 13A or a variant thereof.

67. The pharmaceutical composition of claims 65-66, wherein the AAV is selected from the group consisting of adeno-associated virus-1 (AAV1), AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9 and AAV2i8.

68. The pharmaceutical composition of claims 65-67, wherein the AAV comprises a capsid that detargets the liver.

69. The pharmaceutical composition of any of claims 65-68, wherein the AAV is AAV2i8.

70. The pharmaceutical composition of any of claims 65-69, wherein the AAV comprises a nucleic acid selected from the group consisting of SEQ ID NO: 413-440, or a nucleic acid sequence at least 80% sequence identity to a sequence selected from SEQ ID NO: 413-440, wherein the nucleic acids set forth in SEQ ID NO: 413-440 comprise a CMV promoter of SEQ ID NO: 330, wherein the CMV promoter of SEQ ID NO: 330 is replaced by any of:

- a. a cardiac-specific promoter selected from Table 2A or a variant thereof,
- b. a muscle-specific promoter active in cardiac and skeletal muscle, or
- c. any promoter when a cardiac tissue specific enhancer is present, or a variant thereof

71. The pharmaceutical composition of any of claims 64-69, further comprises a vasodilator.

72. The pharmaceutical composition of any of claims 64-69, further comprises an immune modulator.

73. The pharmaceutical composition of claim 65, wherein the phosphatase inhibitor (I-1) polypeptide is a constitutively active protein (I-1c).

74. The pharmaceutical composition of claim 73, wherein the I-1c is selected from any of:

- a. a polypeptide comprises at least amino acid residues 1-65 of SEQ ID NO: 1 or a functional equivalent thereof;
 - b. a polypeptide comprising at least amino acids 1-54 of SEQ ID NO: 1, wherein the polypeptide is truncated at the C-terminus at amino acid 70, 67, 66, 65, or 61, or 54, and where there is an aspartic acid at position 35 (T35D),
 - c. a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1 or a functional equivalent thereof having at least 85% sequence identity to amino acid residues 1-65 of SEQ ID NO: 1, or
 - d. a polypeptide selected from any of: SEQ ID NOS: 507 or 527-532 or a functional equivalent thereof having at least 85% sequence identity to amino acid residues of any of SEQ ID NOS: 507 or 527-532.
75. The pharmaceutical composition of any of claims 65-74, wherein the nucleic acid sequence encoding a I-1 polypeptide is selected from:
- a. a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an amino acid that is not T,
 - b. a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an acid amino acid selected from any of: aspartic acid (D), glutamic acid (E), asparagine (N), glutamine (Q),
 - c. a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, wherein threonine (T) at position 35 of SEQ ID NO: 1 is replaced with aspartic acid (D), or a conservative amino acid of aspartic acid.
76. The pharmaceutical composition of any of claims 65-74, wherein the nucleic acid sequence encoding the I-1 protein is a codon optimized nucleic acid sequence.
77. The pharmaceutical composition of claim 76, wherein the codon optimized nucleic acid sequence has reduced CpG content as compared to a reference wild type sequence.
78. The pharmaceutical composition of any of claims 65-77, wherein the codon optimized nucleic acid sequence encoding the I-1 polypeptide is selected from any of SEQ ID NO: 385-412, or a nucleic acid sequence having at least 80% sequence identity to a sequence selected from any of SEQ ID NOS: 385-412.
79. Use of an AAV vector according to any one of claims 45-64, for the manufacture of a pharmaceutical composition for the treatment of a subject having cardiomyopathy.

80. The use of the AAV vector of claim 79, wherein the subject with cardiomyopathy has non-ischemic heart failure and/or non-ischemic cardiomyopathy.
81. The use of the AAV vector of claim 79, wherein the subject with cardiomyopathy has a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation.
82. The use of the AAV vector of claim 80, wherein the subject with a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation has a disease or disorder selected from the group consisting of: Arrhythmogenic right ventricular cardiomyopathy, Atrial myxoma, familial, Atrial septal defect ostium primum, Atrial septal defect sinus venosus, Barth syndrome, muscular dystrophy, Buerger disease, Cardioencephalomyopathy, Chromosome 1p36 deletion syndrome, Congenital generalized lipodystrophy type 4, Congenital heart block, Dilated cardiomyopathy, Duchenne muscular dystrophy (DMD), Fabry disease, Familial atrial fibrillation, Familial dilated cardiomyopathy, Familial hypertrophic cardiomyopathy, Familial progressive cardiac conduction defect, Familial thoracic aortic aneurysm and aortic dissection, Fibromuscular dysplasia, Friedreich ataxia, Gaucher disease, Glycogen storage disease (types 2, 3 or 4), His bundle tachycardia, Hurler syndrome, Hypoplastic left heart syndrome, Infantile histiocytoid cardiomyopathy, Intracranial arteriovenous malformation, Isobutyryl-CoA dehydrogenase deficiency, Kallikrein hypertension, Kawasaki disease, Kearns-Sayre syndrome, Left ventricular noncompaction, Limb-girdle muscular dystrophy (types 1B, 2E, 2F, 2M, 2C, 2D), Limited systemic sclerosis, Long QT syndrome 1, Lymphedema and cerebral arteriovenous anomaly, Lymphocytic vasculitis, Microcephaly-cardiomyopathy; Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, Mitochondrial trifunctional protein deficiency, Myotonic dystrophy type 1, Neonatal stroke, Noonan syndromes 1-, 2-, 3-, 4-, 5- and 6, Peripartum cardiomyopathy, Peters plus syndrome, PGM1-CDG, PHACE syndrome, Phospholamban Arg 14 Deletion, Postural orthostatic tachycardia syndrome, Primary carnitine deficiency, Progressive familial heart block (types 1A, 1B and 2), Pseudohypoaldosteronism type 2, Pulmonary arterial hypertension, Pulmonary atresia with intact ventricular septum, Pulmonary atresia with ventricular septal defect, Pulmonary valve stenosis, Pulmonary vein stenosis, Pulmonic stenosis, Renoprival hypertension, Retinal arterial macroaneurysm with supravulvular pulmonic stenosis, Right ventricle hypoplasia, Sarcoidosis, Sengers syndrome, Situs inversus, Sudden Arrhythmia Death Syndrome, Supravulvular aortic stenosis, Swyer syndrome, TANGO2-Related Metabolic Encephalopathy and Arrhythmias, TARP syndrome, Tetralogy of Fallot, Timothy syndrome, Tricuspid atresia, Vici syndrome, VLCAD deficiency and Williams syndrome.
83. The use of the AAV vector of claim 79, wherein the subject with cardiomyopathy has an ischemic cardiomyopathy.
84. The use of the AAV vector of claim 79, wherein the subject with cardiomyopathy has heart failure.

85. The use of the AAV vector of claim 84, wherein the subject with heart failure has a classification of heart failure based upon a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC) or the New York Heart Association (NYHA).
86. The use of the AAV vector of claim 85, wherein the subject with heart failure has a classification of a class III or above class III in the New York Heart Association (NYHA) classification system.
87. Use of an AAV vector according to any one of claims 45-64, for the manufacture of a pharmaceutical composition for the treatment of a subject having a condition or disease associated with heart failure.
88. The use of claim 87, wherein the subject has a classification of congestive heart failure (CHF).
89. The use of claim 87, wherein the classification is based upon a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC) or the New York Heart Association (NYHA).
90. The use of claim 87, wherein the subject has non-ischemic heart failure or non-ischemic cardiomyopathy.
91. The use of claim 87, wherein the subject has ischemic heart failure or ischemic cardiomyopathy.
92. The use of any of claims 79 or 87, wherein the subject has reduced ejection fraction (rEF or HFrEF).
93. A cell comprising the AAV vector of any of claims 45-64.
94. The cell of claim 93, wherein the cell is a cardiac cell or muscle cells.
95. The cell of any of claims 93-94, wherein the cell is in cell culture or a cell present in a subject.
96. An AAV vector according to claims 45-64, a pharmaceutical formulation of any of claims 65-78, or a cell according any of claims 93-95 for use in the treatment of a subject having cardiomyopathy.
97. The AAV vector of claim 96, wherein the subject with cardiomyopathy has non-ischemic heart failure and/or non-ischemic cardiomyopathy.
98. The AAV vector of claim 96, wherein the subject with cardiomyopathy has a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation.
99. The AAV vector of claim 98, wherein the subject with a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation has a disease or disorder selected from the group consisting of: Arrhythmogenic right ventricular cardiomyopathy, Atrial myxoma, familial, Atrial septal defect ostium primum, Atrial septal defect sinus venosus, Barth syndrome, muscular dystrophy, Buerger disease, Cardioencephalomyopathy, Chromosome 1p36 deletion syndrome, Congenital generalized lipodystrophy type 4, Congenital heart block, Dilated cardiomyopathy, Duchenne muscular dystrophy (DMD), Fabry disease, Familial atrial fibrillation, Familial dilated cardiomyopathy, Familial

hypertrophic cardiomyopathy, Familial progressive cardiac conduction defect, Familial thoracic aortic aneurysm and aortic dissection, Fibromuscular dysplasia, Friedreich ataxia, Gaucher disease, Glycogen storage disease (types 2, 3 or 4), His bundle tachycardia, Hurler syndrome, Hypoplastic left heart syndrome, Infantile histiocytoid cardiomyopathy, Intracranial arteriovenous malformation, Isobutyryl-CoA dehydrogenase deficiency, Kallikrein hypertension, Kawasaki disease, Kearns-Sayre syndrome, Left ventricular noncompaction, Limb-girdle muscular dystrophy (types 1B, 2E, 2F, 2M, 2C, 2D), Limited systemic sclerosis, Long QT syndrome 1, Lymphedema and cerebral arteriovenous anomaly, Lymphocytic vasculitis, Microcephaly-cardiomyopathy; Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, Mitochondrial trifunctional protein deficiency, Myotonic dystrophy type 1, Neonatal stroke, Noonan syndromes 1-, 2-, 3-, 4-, 5- and 6, Peripartum cardiomyopathy, Peters plus syndrome, PGM1-CDG, PHACE syndrome, Phospholamban Arg 14 Deletion, Postural orthostatic tachycardia syndrome, Primary carnitine deficiency, Progressive familial heart block (types 1A, 1B and 2), Pseudohypoaldosteronism type 2, Pulmonary arterial hypertension, Pulmonary atresia with intact ventricular septum, Pulmonary atresia with ventricular septal defect, Pulmonary valve stenosis, Pulmonary vein stenosis, Pulmonic stenosis, Renoprival hypertension, Retinal arterial macroaneurysm with supra-ventricular pulmonic stenosis, Right ventricle hypoplasia, Sarcoidosis, Sengers syndrome, Situs inversus, Sudden Arrhythmia Death Syndrome, Supra-ventricular aortic stenosis, Swyer syndrome, TANGO2-Related Metabolic Encephalopathy and Arrhythmias, TARP syndrome, Tetralogy of Fallot, Timothy syndrome, Tricuspid atresia, Vici syndrome, VLCAD deficiency and Williams syndrome.

100. The AAV vector of claim 96, wherein the subject with cardiomyopathy has an ischemic cardiomyopathy.
101. The AAV vector of claim 96, wherein the subject with cardiomyopathy has heart failure.
102. The AAV vector of claim 101, wherein the subject with heart failure has a classification of heart failure based upon a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC) or the New York Heart Association (NYHA).
103. The AAV vector of claim 102, wherein the subject with heart failure has a classification of a class III or above class III in the New York Heart Association (NYHA) classification system.
104. An AAV vector according to claims 45-64, a pharmaceutical formulation of any of claims 65-78, or a cell according any of claims 93-95 for use in the treatment of a patient having heart failure.
105. The AAV vector of claim 104, wherein the subject has a classification of congestive heart failure (CHF).

106. The AAV vector of claim 105, wherein the classification is based upon a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC) or the New York Heart Association (NYHA).
107. The AAV vector of claim 104, wherein the subject has non-ischemic heart failure or non-ischemic cardiomyopathy.
108. The AAV vector of claim 104, wherein the subject has ischemic heart failure or ischemic cardiomyopathy.
109. The AAV vector of claim 96 or 104, wherein the subject has reduced ejection fraction (rEF or HFrEF).
110. The AAV vector of claim 104, wherein the subject with heart failure has a cardiovascular disease or heart disease is selected from any of: congestive heart failure (CHF), left ventricular remodeling, peripheral arterial occlusive disease (PAOD), dilated cardiomyopathy (DCM) including idiopathic dilated cardiomyopathy (IDCM), coronary artery disease, ischemia, arrhythmia, myocardial infarction (MI), abnormal heart contractility, acute (decompensated) heart failure (AHF), abnormal Ca^{2+} metabolism, myocardial ischemia, atherosclerosis, cardiomyopathy, idiopathic cardiomyopathy, genetic disorder induced cardiomyopathy, cardiac arrhythmias, muscular dystrophy, muscle mass abnormality, muscle degeneration, infective myocarditis, drug- or toxin-induced muscle abnormalities, hypersensitivity myocarditis, an autoimmune endocarditis and congenital heart disease and pulmonary heart hypertension.
111. The AAV vector of claim 104, wherein the subject has one or more of:
- non-ischemic heart failure;
 - non-ischemic cardiomyopathy
 - a classification of congestive heart failure (CHF) is based upon a classification system used by the American Heart Association (AH), the American College of Cardiology (ACC) or the New York Heart Association (NYHA); or
 - a reduced ejection fraction (rEF or HFrEF).
112. A method of expressing a phosphatase inhibitor (I-1) polypeptide in a subject with cardiomyopathy, the method comprising introducing into the subject with cardiomyopathy, at least one dose of the AAV vector according to any of claims 45-63,
- wherein the subject with cardiomyopathy has a classification of heart failure,
- wherein the at least one dose of the rAAV is selected from a total dose-range of about 10^{13} vg to about 10^{15} vg, and
- wherein at least twelve months post-administration there is an improvement in the classification of heart failure.

113. The method of claim 112, wherein the classification of heart failure is based upon a classification system used by the American Heart Association (AH), the American College of Cardiology (ACC) or the New York Heart Association (NYHA).
114. The method of claim 112, wherein there is an improvement of classification of at least one level 12 months after administration of the rAAV.
115. The method of claim 112, wherein there is an improvement of classification of at least one level within six months after administration of the rAAV.
116. The method of claim 112, wherein twelve months post-administration there is an improvement of at least 2 levels in the classifications in any one or more of:
 - the American Heart Association (AH),
 - the American College of Cardiology (ACC), or
 - the New York Heart Association (NYHA).
117. The method of any of claims 112-116, further comprising administering an immune modulator concurrent with, or before, or after the administration of the at least one total dose of a rAAV vector.
118. The method of any of claims 112-116, further comprising administering a vasodilator concurrent with, and/or before, and/or after the administration of the at least one total dose of a rAAV vector.
119. The method of any of claims 112-118, wherein the subject has non-ischemic heart failure or non-ischemic cardiomyopathy.
120. The method of any of claims 112-119, wherein the subject with non-ischemic heart failure or non-ischemic cardiomyopathy is has a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation.
121. The method of claim 120, wherein the subject with a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation has a disease or disorder selected from the group consisting of: Arrhythmogenic right ventricular cardiomyopathy, Atrial myxoma, familial, Atrial septal defect ostium primum, Atrial septal defect sinus venosus, Barth syndrome, muscular dystrophy, Buerger disease, Cardioencephalomyopathy, Chromosome 1p36 deletion syndrome, Congenital generalized lipodystrophy type 4, Congenital heart block, Dilated cardiomyopathy, Duchenne muscular dystrophy (DMD), Fabry disease, Familial atrial fibrillation, Familial dilated cardiomyopathy, Familial hypertrophic cardiomyopathy, Familial progressive cardiac conduction defect, Familial thoracic aortic aneurysm and aortic dissection, Fibromuscular dysplasia, Friedreich ataxia, Gaucher disease, Glycogen storage disease (types 2, 3 or 4), His bundle tachycardia, Hurler syndrome, Hypoplastic left heart syndrome, Infantile histiocytoid cardiomyopathy, Intracranial arteriovenous malformation, Isobutyryl-CoA dehydrogenase deficiency, Kallikrein hypertension, Kawasaki disease, Kearns-Sayre syndrome, Left ventricular noncompaction, Limb-girdle muscular dystrophy (types 1B, 2E, 2F, 2M, 2C, 2D), Limited systemic sclerosis, Long QT syndrome 1, Lymphedema and cerebral arteriovenous anomaly, Lymphocytic vasculitis, Microcephaly-cardiomyopathy, Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, Mitochondrial trifunctional protein deficiency, Myotonic

dystrophy type 1, Neonatal stroke, Noonan syndromes 1 -, 2-, 3-, 4-, 5- and 6, Peripartum cardiomyopathy, Peters plus syndrome, PGM1-CDG, PHACE syndrome, Phospholamban Arg 14 Deletion, Postural orthostatic tachycardia syndrome, Primary carnitine deficiency, Progressive familial heart block (types 1A, 1B and 2), Pseudohypoaldosteronism type 2, Pulmonary arterial hypertension, Pulmonary atresia with intact ventricular septum, Pulmonary atresia with ventricular septal defect, Pulmonary valve stenosis, Pulmonary vein stenosis, Pulmonic stenosis, Renoprival hypertension, Retinal arterial macroaneurysm with supra-ventricular pulmonic stenosis, Right ventricle hypoplasia, Sarcoidosis, Sengers syndrome, Situs inversus, Sudden Arrhythmia Death Syndrome, Supravalvular aortic stenosis, Swyer syndrome, TANGO2-Related Metabolic Encephalopathy and Arrhythmias, TARP syndrome, Tetralogy of Fallot, Timothy syndrome, Tricuspid atresia, Vici syndrome, VLCAD deficiency and Williams syndrome.

122. The method of any of claims 111-117, wherein the subject with heart failure is an ischemic cardiomyopathy.
123. The method of any of claims 111-120, wherein the subject with heart failure has a cardiovascular disease or heart disease is selected from any of: congestive heart failure (CHF), left ventricular remodeling, peripheral arterial occlusive disease (PAOD), dilated cardiomyopathy (DCM) including idiopathic dilated cardiomyopathy (IDCM), coronary artery disease, ischemia, arrhythmia, myocardial infarction (MI), abnormal heart contractility, acute (decompensated) heart failure (AHF), abnormal Ca^{2+} metabolism, myocardial ischemia, atherosclerosis, cardiomyopathy, idiopathic cardiomyopathy, genetic disorder induced cardiomyopathy, cardiac arrhythmias, muscular dystrophy, muscle mass abnormality, muscle degeneration, infective myocarditis, drug- or toxin-induced muscle abnormalities, hypersensitivity myocarditis, an autoimmune endocarditis and congenital heart disease and pulmonary heart hypertension.
124. The method of any of claims 111-122, wherein the subject has reduced ejection fraction (rEF or HFrEF).
125. The method of any of claims 111-123, wherein the heart failure comprises ischemia, arrhythmia, myocardial infarction, abnormal heart contractility, or abnormal Ca^{2+} metabolism.
126. The method of any of claims 111-124, wherein the administration is into the lumen of the coronary artery of the heart of the patient.
127. The method of any of claims 111-125, wherein the at least one dose is a total dose-range of about 10^{13} vg to about 10^{15} vg., administered in one dose or 2 to 5 sub-doses.
128. The method of any of claims 111-126, wherein the total dose is administered as any of the following administration methods:
 - a. over a period of time of about 20 minutes to about 30 minutes,

- b. administered in a series of sub-doses, wherein each sub-dose is administered over a period of time of about 1 minute to about 5 minutes,
- c. administered in a series of five sub-doses, each sub-dose is administered over a period of time of about 1 minute to about 5 minutes, and wherein the five sub-doses are administered over a period of about 20 minutes to about 30 minutes.

CLAIMS

1. Use of an rAAV vector comprising a nucleic acid sequence encoding a phosphatase inhibitor (I-1) protein that inhibits phosphatase activity in the preparation of a medicament for the treatment of heart failure in a patient, in which at least one total dose of the rAAV is to be administered into heart cells of the patient having a classification of congestive heart failure (CHF), in which the at least one dose of the rAAV is selected from a total dose-range of about 10^{13} vg to about 10^{15} vg and in which at least twelve months post-administration there is an improvement in the classification of congestive heart failure.
2. Use according to Claim 1, in which the classification is based upon a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC), Minnesota LIVING WITH HEART FAILURE® Questionnaire (MLHFQ), Kansas City Cardiomyopathy questionnaire (KCCQ), or the 2016 European Society of Cardiology guidelines (ESCG), the Japanese heart failure Society (JHFS) guidelines, The Japanese Circulation Society (JCS) Guidelines, or, the New York Heart Association (NYHA).
3. Use according to Claim 1 or 2, in which there is an improvement in the classification of at least one level within 6 or 12 months after administration of the rAAV, or in which twelve months post-administration there is an improvement of at least 2 levels in the Classification.
4. Use according to Claim 1, 2 or 3, in which the classification system is NYHA and the level of classification is selected from the group consisting of: Class I, Class II, Class III and Class IV, or in which the classification system is the American College of Cardiology/American Heart Association (ACC/AHA) complementary staging system and the level of classification is selected from the group consisting of: Stages A, Stage B, Stage C, Stage D, or in which the classification system is KCCQ and the level of classification is a KQQC overall summary score range selected from the group consisting of: KCCQ fair to excellent scores of 50 to 100, very poor to fair scores of 0 to 49, good to excellent scores of 75 to 100 and very poor to good scores of 0 to 74.
5. Use of an rAAV vector comprising a nucleic acid sequence encoding a phosphatase inhibitor (I-1) protein that inhibits phosphatase activity in the preparation of a medicament for the treatment of cardiomyopathy in a patient, in which at least one total dose of rAAV is to be administered into heart cells of the patient, in which the at least one dose of the rAAV is selected from a total dose-range of about 10^{13} vg to about 10^{15} vg, in which at least twelve

months post-administration there is an improvement in the at least one parameter from a baseline level in the patient and in which the at least one parameter is selected from the group consisting essentially of:

- (a) ejection fraction (EF),
- 5 (b) end systolic volume (ESV)
- (c) cardiac contractility, selected from ejection fraction (EF) and fractional shortening (FS)
- (d) cardiac volumes selected from any of: end diastolic volume (DV) and end systolic volume (ESV),
- 10 (e) functional criteria, selected from any of: a 6-minute walk test (6MWT), exercise and VO₂max;
- (f) BNP level,
- (g) Pro-BNP level
- (h) biomarker level, in which the biomarker level is selected from the group of:
- 15 troponin, serum creatinine, cystatin-C, or hepatic transaminases,
- (i) Patient-reported outcomes (PROs), such as reduced symptoms, health-related quality of life (HRQOL), or patient perceived health status and
- (j) decrease in any of: mortality risk due to heart failure, reduced hospitalization due to heart failure symptoms, or therapeutic intervention for treatment of heart failure.
- 20 6. Use according to Claim 5, in which the improvement is selected from any of:
- (a) at least a 5% or more increase in ejection fraction from baseline,
- (b) at least a 10% decrease, or at least a 20ml decrease in end systolic volume from baseline,
- (c) at least a 50-meter increase in 6-minute walk test from baseline,
- 25 (d) at least a 40% decrease in BNP levels (pg/ml) in the blood from baseline,
- (e) at least a 35% decrease in pro-BNP levels (pg/ml) in the blood from baseline,
- (f) at least a 10% reduction in a biomarker selected from: troponin, serum creatinine, cystatin-C, or hepatic transaminases from a baseline level of the same biomarker,

(g) at least a 1.5ml/kg/min increase in myocardial oxygen consumption (MVO₂) from baseline, or

(h) a discharge from hospital due to improved HF symptoms, or a reduced intervention selected from a decrease in the use of any of: inotropes, vasodilators, diuretics due to improved HF symptoms in the subject.

7. Use according to any preceding claim, in which the total dose is to be administered as any of the following administration methods:

(a) over a period of time of about 20 minutes to about 30 minutes,

(b) to be administered in a series of sub-doses, in which each sub-dose is to be administered over a period of time of about 1 minute to about 5 minutes,

(c) to be administered in a series of five sub-doses, each sub-dose is to be administered over a period of time of about 1 minute to about 5 minutes and in which the five sub-doses are to be administered over a period of about 20 minutes to about 30 minutes.

8. Use according to any of Claims 1 to 6, in which there rAAV vector comprises a capsid that detargets the liver.

9. Use according to any preceding claim, in which the rAAV is selected from the group consisting of AAV1, AAV2, AAV6, AAV8, AAV9, AAV2i8, rh10, AAV2.5 and AAV2G9.

10. Use according to any preceding claim, in which at least one total dose of the rAAV is 10^{13} vg, 3×10^{13} vg, 10^{14} vg, 3×10^{14} vg, or, 10^{15} vg.

11. Use according to Claim 1, in which the I-1c is selected from any of:

(a) a polypeptide comprises at least amino acid residues 1-54 of SEQ ID NO: 1, in which SEQ ID NO: 1 is truncated at the C-terminus at amino acid 70, 67, 66, 65, or 61, or 54 and where there is an aspartic acid at position 35 (T35D),

(b) a polypeptide comprising amino acids 1-54 of SEQ ID NO:1 or a functional fragment thereof, in which the functional fragment has at least 85% sequence identity to amino acid residues 1-54 of SEQ ID NO: 1, or truncated at the C-terminus at amino acid 70, 67, 66, 65, or 61, or 54 and where there is an aspartic acid at position 35 (T35D),

(c) a constitutively active protein (I-1c), or

(d) a polypeptide encoded by a codon-optimized I-1C nucleic acid.

12. Use according to any preceding claim, in which the rAAV genome comprises nucleic acid sequence selected from the group consisting of: SEQ ID NO: 413-441.

13. Use according to Claim 1, in which the nucleic acid sequence encoding the I-1 polypeptide is selected from

(a) a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, in which threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an amino acid that is not T,

(b) a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, in which threonine (T) at position 35 of SEQ ID NO: 1 is replaced with an acid amino acid selected from any of: aspartic acid (D), glutamic acid (E), asparagine (N), glutamine (Q),

(c) a nucleic acid sequence encoding a polypeptide comprising amino acids 1-65 of SEQ ID NO: 1, in which threonine (T) at position 35 of SEQ ID NO: 1 is replaced with aspartic acid (D), or a conservative amino acid of aspartic acid.

(d) any of SEQ ID NO: 385-412, or a nucleic acid sequence having at least 80% sequence identity to SEQ ID NO: 385-412.

14. Use according to any preceding claim, in which the subject with cardiomyopathy has non-ischemic heart failure and/or non-ischemic cardiomyopathy, or in which the subject with cardiomyopathy has a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation.

15. Use according to Claim 1, in which the subject with a congenital cardiomyopathy or a genetic disorder with a cardiac manifestation has a disease or disorder selected from the group consisting of: Arrhythmogenic right ventricular cardiomyopathy, Atrial myxoma, familial, Atrial septal defect ostium primum, Atrial septal defect sinus venosus, Barth syndrome, muscular dystrophy, Buerger disease, Cardioencephalomyopathy, Chromosome 1p36 deletion syndrome, Congenital generalized lipodystrophy type 4, Congenital heart block, Dilated cardiomyopathy, Duchenne muscular dystrophy (DMD), Fabry disease, Familial atrial fibrillation, Familial dilated cardiomyopathy, Familial hypertrophic cardiomyopathy, Familial progressive cardiac conduction defect, Familial thoracic aortic aneurysm and aortic dissection,

Fibromuscular dysplasia, Friedreich ataxia, Gaucher disease, Glycogen storage disease (types 2, 3 or 4), His bundle tachycardia, Hurler syndrome, Hypoplastic left heart syndrome, Infantile histiocytoid cardiomyopathy, Intracranial arteriovenous malformation, Isobutyryl-CoA dehydrogenase deficiency, Kallikrein hypertension, Kawasaki disease, Kearns-Sayre syndrome, Left ventricular noncompaction, Limb-girdle muscular dystrophy (types 1B, 2E, 2F, 2M, 2C, 2D), Limited systemic sclerosis, Long QT syndrome 1, Lymphedema and cerebral arteriovenous anomaly, Lymphocytic vasculitis, Microcephaly-cardiomyopathy; Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, Mitochondrial trifunctional protein deficiency, Myotonic dystrophy type 1, Neonatal stroke, Noonan syndromes 1 -, 2-, 3-, 4-, 5- and 6, Peripartum cardiomyopathy, Peters plus syndrome, PGM1-CDG, PHACE syndrome, Phospholamban Arg 14 Deletion, Postural orthostatic tachycardia syndrome, Primary carnitine deficiency, Progressive familial heart block (types 1A, 1B and 2), Pseudohypoaldosteronism type 2, Pulmonary arterial hypertension, Pulmonary atresia with intact ventricular septum, Pulmonary atresia with ventricular septal defect, Pulmonary valve stenosis, Pulmonary vein stenosis, Pulmonic stenosis, Renoprival hypertension, Retinal arterial macroaneurysm with supra-ventricular pulmonic stenosis, Right ventricle hypoplasia, Sarcoidosis, Sengers syndrome, Situs inversus, Sudden Arrhythmia Death Syndrome, Supra-ventricular aortic stenosis, Swyer syndrome, TANGO2-Related Metabolic Encephalopathy and Arrhythmias, TARP syndrome, Tetralogy of Fallot, Timothy syndrome, Tricuspid atresia, Vici syndrome, VLCAD deficiency and Williams syndrome.

16. Use according to any preceding claim, in which at least twelve months post-administration of the rAAV there is an improvement of at least one class in a classification of heart failure from a baseline level, in which the classification of heart failure is assessed by at least one of the following:

- 25 (a) a classification system used by the American Heart Association (AHA), the American College of Cardiology (ACC), the 2016 European Society of Cardiology guidelines (ESC), the Japanese heart failure Society (JHFS) guidelines, The Japanese Circulation Society (JCS) Guidelines, or, the New York Heart Association (NYHA); or equivalent thereof, or
- 30 (b) a health-related quality of life (HRQL) questionnaire selected from the group consisting from any of: Minnesota LIVING WITH HEART FAILURE® Questionnaire (MLHFQ), or Kansas City Cardiomyopathy questionnaire (KCCQ), Chronic Heart

Failure Questionnaire (CHFQ), Quality of Life Questionnaire for Severe Heart Failure (QLQ-SHF), Left Ventricular Dysfunction (LVD-36) questionnaire and the Left Ventricular Disease Questionnaire (LVDQ).

17. Use according to any preceding claim, in which the subject is to be administered a vasodilator concurrent with, and/or before, and/or after the administration of the at least one total dose of a rAAV vector, and/or in which the subject is to be administered an immune modulator concurrent with, or before, or after the administration of the at least one total dose of a rAAV vector.
18. A pharmaceutical composition comprising an AAV vector that comprises a codon optimized I-Ic nucleic sequence selected from any of SEQ ID NO: 385-412, or nucleic acid sequence having at least 80% sequence identity to SEQ ID NOS: 385-412.
19. An adeno-associated virus (AAV) vector comprising a nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide operably linked to a promoter selected from any of:
 - a cardiac-specific promoter selected from Table 2A or a variant thereof,
 - a muscle-specific promoter active in cardiac and skeletal muscle, or a variant thereof, or any promoter when a cardiac tissue specific enhancer is present.
20. An AAV vector according to Claim 19, in which muscle-specific promoter active in cardiac and skeletal muscle is selected from Table 5A or Table 13A or a variant thereof.
21. A pharmaceutical composition comprising:
 - (i) adeno-associated virus (AAV) vector comprising a nucleic acid sequence encoding a Phosphatase inhibitor (I-1) polypeptide operably linked to any one of:
 - (a) a cardiac-specific promoter selected from Table 2A or a variant thereof,
 - (b) a muscle-specific promoter active in cardiac and skeletal muscle, or
 - (c) any promoter when a cardiac tissue specific enhancer is present, or a variant thereof; and
 - (ii) a pharmaceutically acceptable carrier.
22. A cell comprising an AAV vector according to Claim 19 or 20.

23. Use of an AAV vector according to Claim 19 or 20 in the preparation of a medicament for expressing a phosphatase inhibitor (I-1) polypeptide in a subject with cardiomyopathy, in which at least one dose of the AAV vector is to be introduced into the subject,

in which the subject with cardiomyopathy has a classification of heart failure,

5 in which the at least one dose of the rAAV is selected from a total dose-range of about 10^{13} vg to about 10^{15} vg and

in which at least twelve months post-administration there is an improvement in the classification of heart failure.