CLAIMS

~~1. An acylated ghrelin molecule for use in the treatment of Acute Heart Failure (AHF) in an individual.~~

1~~2~~. Use of an acylated ghrelin molecule in the manufacture of a medicament for the treatment of Acute Heart Failure (AHF) in an individual.

~~3. A method for the treatment of Acute Heart Failure (AHF) in an individual, the method comprising the step of administering to the individual an acylated ghrelin molecule.~~

~~4. The acylated ghrelin molecule for use according to Claim 1, or the use according to Claim 2, or the method according to Claim 3, wherein the AHF is AHF of the left side of the heart or AHF of the right side of the heart.~~

2~~5~~. The ~~acylated ghrelin molecule for use according to Claim 1 or 4, or the~~ use according to Claim 1~~2 or 4~~, ~~or the method according to Claim 3 or 4,~~ wherein the AHF is selected from the group comprising: Acute Decompensated Heart Failure (ADHF); AHF associated with hypertension; tachycardia-mediated AHF; AHF associated with pulmonary edema; cardiogenic shock AHF; or severe cardiogenic shock AHF.

3~~6~~. The ~~acylated ghrelin molecule for use or the~~ use ~~or the method~~ according to Claim 2~~5~~, wherein the Acute Decompensated Heart Failure (ADHF) is Acute Decompensated Chronic Heart Failure (ADCHF) or congestive ADHF, preferably Acute Decompensated Chronic Heart Failure (ADCHF).

~~7. The acylated ghrelin molecule for use or the use or the method according to Claim 6, wherein the Acute Decompensated Chronic Heart Failure (ADCHF) is severe ADCHF.~~

~~8. The acylated ghrelin molecule for use or the use or the method according to Claim 6 or 7, wherein the AHF is ADCHF or severe ADCHF and the individual has had Chronic Heart Failure (CHF) for about one year or more, preferably about two years or more or about three years or more.~~

~~9. The acylated ghrelin molecule for use or the use or the method according to Claim 6 or 7, wherein the AHF is ADCHF or severe ADCHF and the individual has had Chronic Heart Failure (CHF) for about one year or less.~~

4~~10~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-9, or the~~ use according to any one of Claims 1-3~~2, or 4-9, or the method according to any one of Claims 3-9~~, wherein the AHF is not associated with a myocardial infarction.

5~~11~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-10, or the~~ use according to any one of Claims 1-4~~2 or 4-10~~, ~~or the method according to any one of Claims 3-10,~~ wherein the AHF is not *de novo* AHF.

6~~12~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-11, or the~~ use according to any one of Claims 1-5~~2 or 4-11~~, ~~or the method according to any one of Claims 3-11,~~ wherein after administration of the ghrelin molecule the individual exhibits one or more parameters from the group comprising: an increased heart output; and/or an increased heart contraction; and/or an increased heart stroke volume; and/or an increased ventricular function; and/or an increased ventricular ejection fraction; and/or reduced troponin I phosphorylation; and/or an increased calcium sensitivity; and/or reduced intracellular cAMP; and/or improved renal function; and/or improved estimated glomerular filtration rate (eGFR); and/or improved dyspnea; and/or improved edema; and/or reduced biomarkers; and/or reduced hypotension; and/or resolution of cardiogenic shock; and/or reduced dizziness; and/or reduced light-headedness; and/or a reduced arterio venous oxygen (AVO2) difference; and/or an increase in pulmonary blood flow (PBF); and/or a reduced estimated systemic vascular resistance (eSVR); and/or reduced pulmonary capillary wedge pressure; and/or reduced left ventricular end-diastolic pressure; and/or reduced left ventricular end-diastolic volume; and/or reduced pulmonary artery pressure; and/or reduced central venous pressure.

~~13. The acylated ghrelin molecule for use or the use or the method according to Claim 12, wherein the one or more parameters are from the group comprising: an increased heart output; and/or a reduced arterio venous oxygen (AVO2) difference; and/or an increase in pulmonary blood flow (PBF); and/or a reduced estimated systemic vascular resistance (eSVR).~~

14. The acylated ghrelin molecule for use or the use or the method according to Claim 12 or 13, wherein the heart output is increased if: the heart output volume is about 1.5 litres/minute or more, preferably about 5.2 litres/minute or more; and/or the heart output volume increases by about 0.1 litres/minute or more, preferably about 0.5 litres/minute or more; more preferably about 1.15 litres/minute or more; and/or the heart output volume increases by about 5% or more.

15. The acylated ghrelin molecule for use or the use or the method according to Claim 12 or 14, wherein the heart contraction is increased if there is an increase of absolute percent fractional shortening of about 2% or more, preferably about 3% or more; and/or an increase of relative percent fractional shortening of about 20% or more, preferably about 42% or more.

16. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 12, 14 or 15, wherein the heart stroke volume is increased if: the heart stroke volume is about 30 ml or more, preferably about 69 ml or more; more preferably about 79 ml or more; and/or, the heart stroke volume increases by about 3 ml or more; and/or the heart stroke volume increases by about 5% or more, preferably about 15% or more, more preferably about 25% or more.

17. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 12 or 14-16, wherein the troponin I phosphorylation is reduced by about 20% or more.

18. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 12 or 14-17, wherein the intracellular cAMP is reduced by about 20% or more.

19. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 12 or 14-18, wherein the ventricular ejection fraction is increased if there is an increase of absolute percentage of about 2% or more; and/or an increase of relative percentage of about 5% or more, preferably about 10% or more.

20. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 12-19, wherein the arterio venous oxygen (AVO2) difference is reduced by about 2% or more, preferably about 7% or more.

~~21. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 12-20, wherein the pulmonary blood flow (PBF) level is increased by about 0.1 litre/minute or more, preferably about 0.8 litre/minute or more or about 1 litre/minute or more.~~

~~22. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 12-21, wherein the estimated systemic vascular resistance (eSVR) is reduced by about 100 dyn*s/cm^{-5} or more, preferably about 300 dyn*s/cm^{-5} or more.~~

7~~23~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-22, or the~~ use according to any one of Claims 1-6~~2 or 4-22~~, ~~or the method according to any one of Claims 3-22,~~ wherein the AHF is associated with one or more factors of the group comprising: spontaneous worsening of chronic heart failure; an infection; and/or an allergic reaction; and/or a blood clot; and/or surgery; and/or cardiovascular disease; and/or lung disease; and/or cardiomyopathy; and/or sleep apnea; and/or alcohol consumption; and/or recreational drug consumption; and/or anaemia; and/or dyslipidemia; and/or an overactive thyroid; and/or Paget's disease; and/or hypertension (such as pulmonary hypertension); and/or prescription medication consumption; and/or smoking; and/or high blood pressure; and/or kidney dysfunction; and/or diabetes; and/or congenital heart defects; and/or lifestyle choices; and/or an irregular heartbeat; and/or rapid heartbeat; and/or slow heartbeat; and/or inflammation; and/or toxins; and/or autoimmune disease; and/or infiltrative disease; and/or connective tissue disease; and/or metabolic disease; and/or endocrine disease; and old age; and/or hereditary genetic mutations; and/or pregnancy.

~~24. The acylated ghrelin molecule for use or the use or the method according to Claim 23, wherein the AHF is associated with one or more factors of the group comprising: spontaneous worsening of chronic heart failure; infection; diabetes; and/or lifestyle choices (such as, obesity and/or a sedentary lifestyle).~~

~~25. The acylated ghrelin molecule for use or the use or the method according to Claim 23 or 24, wherein the AHF is associated with hypertension~~

826. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-25, or the~~ use according to any one of Claims 1-72 ~~or 4-25~~, ~~or the method according to any one of Claims 3-25,~~ wherein the AHF comprises one or more of the symptoms of the group comprising: chest pain; and/or a cough; and/or shock (such as, cardiogenic shock); and/or high blood pressure; and/or oliguria; and/or anuria; and/or fatigue; and/or shortness of breath (dyspnea); and/or hypoxemia; and/or rapid breathing (tachypnea); and/or tachycardia; and/or ischemia; and/or edema (such as, a worsening edema); and/or impaired renal function (such as, worsening renal function); and/or low blood pressure; and/or organ failure (such as liver failure and/or kidney failure); and/or cold extremities; and/or numb extremities; and/or muscle fatigue; and/or nausea; and/or vomiting; and/or weight loss (such as anorexia); and/or pulmonary edema; and/or discomfort of the lower body; and/or peripheral swelling; and/or hypo-perfusion; and/or swelling of the lower body; and/or swelling of the heart; and/or weight gain (such as, sudden weight gain); and/or weight loss; and/or cachexia; and/or elevated neck blood vessels (such as an elevated neck blood vein and/or jugular venous distension); and/or hepatomegaly; and/or dizziness; and/or fainting (also known as syncope); and/or an altered mental state (for example, anxiety and/or confusion and/or depression); and/or loss of appetite; hypotension; and/or arrhythmia; and/or difficulty sleeping; and/or discomfort when lying flat; and/or sleep apnea.

~~27. The acylated ghrelin molecule for use or the use or the method according to Claim 26, wherein the AHF comprises one or more of the symptoms of the group comprising: dyspnea (such as, dyspnea at rest); and/or hypoxemia; and/or an edema (such as, a worsening edema); and/or sudden weight gain; and/or impaired renal function (such as, worsening renal function); and/or low blood pressure; and/or dizziness; and/or cardiogenic shock.~~

~~28. The acylated ghrelin molecule for use or the use or the method according to Claim 26, wherein the AHF comprises one or more of the symptoms of the group comprising: dyspena; and/or discomfort when lying flat; and/or rapid breathing; and/or anxiety; and/or hypoxemia; and/or high blood pressure.~~

~~29. The acylated ghrelin molecule for use or the use or the method according to Claim 26, wherein the AHF comprises one or more of the symptoms of the group comprising: edema (such as, a worsening edema); weight gain; and/or elevated neck vein; and/or hepatomegaly.~~

~~30. The acylated ghrelin molecule for use according to any one of Claims 1 or 4-29, or the use according to any one of Claims 2 or 4-29, or the method according to any one of Claims 3-29, wherein one or more symptoms develop over a period of about one month or less, preferably about seven days or less; more preferably a period of about seven days to about one day.~~

9~~31~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-30, or the~~ use according to any one of Claims 1-8~~2 or 4-30~~, ~~or the method according to any one of Claims 3-30,~~ wherein the individual is diagnosed as having AHF using one or more of the procedures of the group comprising: an X-ray; and/or a blood test; and/or an electrocardiogram (ECG); and/or based on the medical history of the individual; and/or a positron emission tomography (PET) scan; and/or multigated acquisition (MUGA) scan; and/or scintigraphy; and/or an echocardiogram; and/or an angiogram; and/or hemodynamic measurement; and/or a computerised tomography (CT) scan; and/or a physical examination of symptoms; and/or measuring biomarkers (such as serum natriuretic peptides and/or plasma natriuretic peptides); and/or, a magnetic resonance imaging (MRI) scan.

~~32. The acylated ghrelin molecule for use or the use or the method according to Claim 31, wherein the individual is diagnosed as having AHF using one or more of the procedures of the group comprising: based on the medical history of the individual; and/or a physical examination of symptoms; and/or an echocardiogram; and/or measuring serum natriuretic peptides.~~

~~33. The acylated ghrelin molecule for use or the use or the method according to Claim 32, wherein the biomarkers are one or more selected of the group comprising: serum natriuretic peptides; and/or sST2 cardiac biomarker; and/or mid-regional pro-adrenomedullin (MR-proADM); and/or lactate.~~

~~34. The acylated ghrelin molecule for use or the use or the method according to Claim 33, wherein the serum natriuretic peptides comprise B-type natriuretic peptide (BNP) and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP); and/or mid-regional pro-atrial natriuretic peptide (MR-proANP).~~

~~35. The acylated ghrelin molecule for use or the use or the method according to Claim 34, wherein the individual is diagnosed as having AHF if BNP is 50 ng/litre or more, preferably about 100 ng/litre or more; and/or NT-proBNP is 250 ng/litre or more, preferably about 300 ng/litre or more.~~

~~36. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 31-35, wherein the hemodynamic measurement is one or more of the group comprising: measurement of systolic blood pressure; and/or measurement of cardiac index; and/or measurement of pulmonary capillary wedge pressure.~~

~~37. The acylated ghrelin molecule for use or the use or the method according to Claim 36, wherein the hemodynamic measurement is the measurement of cardiac index and the cardiac index is about five litres/minute/metre^2 or less, preferably about two litres/minute/metre^2 or less or about 1.8 litres/minute/metre^2 or less.~~

~~38. The acylated ghrelin molecule for use or the use or the method according to Claim 36 or 37, wherein the hemodynamic measurement is the measurement of pulmonary capillary wedge pressure and the pulmonary capillary wedge pressure is about 10 mmHg or more.~~

10~~39~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-38, or the~~ use according to any one of Claims 1-9~~2 or 4-38~~, ~~or the method according to any one of Claims 3-38,~~ wherein after administration of the ghrelin molecule the individual does not exhibit one or more parameters of the group comprising: an increased heart rate; and/or tachycardia; and/or a decreased blood pressure; and/or hypotension; and/or an increased oxygen demand; and/or ischemia; and/or increased plasma troponin T; and/or heart arrhythmias; and/or affected calcium transients.

~~40. The acylated ghrelin molecule for use or the use or the method according to Claim 39, wherein after administration of the ghrelin molecule the individual does not exhibit one or more parameters of the group comprising: hypotension; and/or ischemia; and/or heart arrhythmias; and/or tachycardia.~~

41. The acylated ghrelin molecule for use or the use or the method according to Claim 39, wherein the heart rate is increased by about 5 heart beats/minute or more and/or is about 100 heart beats/minute or more.

42. The acylated ghrelin molecule for use or the use or the method according to Claim 39 or 41, wherein tachycardia is an increase in heart rate of about 10 heart beats/minute or more; and/or a heart rate of about 110 heart beats/minute or more.

43. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 39, 41 or 42, wherein the blood pressure is decreased by about 5 mmHg or more, preferably about 20 mmHg or more, more preferably 20 mmHg to 80 mmHg.

44. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 39 or 41-43, wherein hypotension is a blood pressure of about 90 mmHg or less, preferably about 80 mmHg or less.

45. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 39 or 41-44, wherein the heart arrhythmia is selected from the group comprising: ventricular arrhythmia; supra-ventricular arrhythmia; ectopic atrial tachycardia; atrial flutter; sinus bradycardia; atrial ventricular block (AV block); and atrial fibrillation.

46. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 39 or 41-45, wherein the ischemia comprises a change in an electrocardiogram (ECG) and/or increased plasma troponin T.

47. The acylated ghrelin molecule for use or the use or the method according to Claim 46, wherein the change in an electrocardiogram (ECG) comprises one or more of the group comprising: ST elevations; and/or ST depressions; and/or T wave changes.

48. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 39-47, wherein the plasma troponin T is increased by about 40% or more, preferably about 100% or more.

~~49. The acylated ghrelin molecule for use or the use or the method according to any one of Claims 33-48, wherein the calcium transient comprises no change in the calcium transient amplitude.~~

1150. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-49, or the~~ use according to any one of Claims 1-102 ~~or 4-49~~, ~~or the method according to any one of Claims 3-49,~~ wherein the acylated ghrelin molecule comprises one or more of the group comprising: a modified ghrelin; and/or a ghrelin fusion molecule; and/or a ghrelin fragment; and/or a ghrelin variant; and/or a ghrelin derivative; and/or, wildtype ghrelin.

1251. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-50, or the~~ use according to any one of Claims 1-112 ~~or 4-50~~, ~~or the method according to any one of Claims 3-50,~~ wherein the ghrelin molecule comprises one or more of the group comprising: a synthetic ghrelin molecule; and/or a recombinant ghrelin molecule; and/or, an endogenous ghrelin molecule.

1352. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-51, or the~~ use according to any one of Claims 1-122 ~~or 4-51~~, ~~or the method according to any one of Claims 3-51,~~ wherein the ghrelin molecule is to be administered once or more each day, preferably twice each day.

1453. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-52, or the~~ use according to any one of Claims 1-132 ~~or 4-52~~, ~~or the method according to any one of Claims 3-52,~~ wherein the ghrelin molecule is to be administered by infusion.

~~54. The acylated ghrelin molecule for use or the use or the method according to Claim 53, wherein the infusion is over a period of about 10 minutes or more, preferably about 120 minutes.~~

1555. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-54, or the~~ use according to any one of Claims 1-142 ~~or 4-54~~, ~~or the method according to any one of Claims 3-54,~~ wherein the individual is aged 18 years or older, preferably 65 years or older.

16~~56~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-55, or the~~ use according to any one of Claims 1-15~~2 or 4-55~~, ~~or the method according to any one of Claims 3-55,~~ wherein the ghrelin molecule is to be administered before surgery, and/or during surgery, and/or after surgery.

17~~57~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-56, or the~~ use according to any one of Claims 1-16~~2 or 4-56~~, ~~or the method according to any one of Claims 3-56,~~ wherein the individual is to be administered with one or more additional therapeutic agents.

18~~58~~. The ~~acylated ghrelin molecule for use according to any one of Claims 1 or 4-57, or the~~ use according to any one of Claims 1-17~~2 or 4-57, or the method according to any one of Claims 3-57~~, wherein the ghrelin molecule is in a composition, preferably a pharmaceutical composition.

~~59. The acylated ghrelin molecule for use or the use or the method according to Claim 58, wherein the composition comprises a pharmaceutically acceptable excipient.~~

19~~60~~. The ~~acylated ghrelin molecule for use or the~~ use ~~or the method~~ according to Claim 18~~58 or 59~~, wherein the composition comprises one or more additional therapeutic agents.

20~~61~~. The ~~acylated ghrelin molecule for use or the~~ use ~~or the method~~ according to any one of Claims 17-19~~57-60~~, wherein ~~the~~ any additional therapeutic agent is one or more therapeutic agent selected from the group comprising: angiotensin-converting enzyme (ACE) inhibitors; and/or angiotensin II receptor blockers; and/or vasopressin receptor antagonists; and/or beta blockers; and/or an inodilator (in particular, mirinone and/or enoximone and/or dobutamine and/or levosimendan); and/or omecamtiv mecarbil; and/or renin antagonist; and/or relaxin; and/or ularitide; and/or digoxin (Lanoxin); and/or vasodilators; and/or angiotensin II receptor antagonists (such as valsartan); and/or aspirin; and/or statins; and/or antihypertensive drugs (such as sacubitril); and/or calcium sensitisers; and/or ivabradine; and/or diuretics; and/or vasopressor (such as noradrenaline, dopamine, vasopressin, and/or angiotensin II); and/or adenosine antagonists; and/or aldosterone antagonists.

62. A composition comprising an acylated ghrelin molecule and one or more therapeutic agents selected from the list comprising: angiotensin-converting enzyme (ACE) inhibitors; and/or angiotensin II receptor blockers; and/or vasopressin receptor antagonists; and/or beta blockers; and/or an inodilator (in particular, mirinone and/or enoximone and/or dobutamine and/or levosimendan); and/or omecamtiv mecarbil; and/or renin antagonist; and/or relaxin; and/or ularitide; and/or digoxin (Lanoxin); and/or vasodilators; and/or angiotensin II receptor antagonists (such as valsartan); and/or aspirin; and/or statins; and/or antihypertensive drugs (such as sacubitril); and/or calcium sensitisers; and/or ivabradine; and/or diuretics; and/or vasopressor (such as noradrenaline, dopamine, vasopressin, and/or angiotensin II); and/or adenosine antagonists; and/or aldosterone antagonists.

63. The composition according to Claim 62, comprising one or more therapeutic agents selected from the list comprising: relaxin; and/or ularitide; and/or inodilators; and/or vasopressors; and/or vasodilators.

64. The composition according to Claim 62 or 63 comprising a pharmaceutically acceptable excipient.

65. A composition as defined in any one of Claims 62-64 for the use as defined in any one of Claims 1-61.

66. A use as defined in any one of Claims 1-61 of a composition as defined in any one of Claims 62-64.

67. A method as defined in any one of Claims 1-61 comprising the step of administering to the individual a composition as defined in any one of Claims 62-64.

68. A kit of parts comprising an acylated ghrelin molecule as defined in any of Claims 1-61 and/or composition as defined in any one of Claims 62-64.

69. The kit of parts according to Claim 68 comprising instructions for the use of the acylated ghrelin molecule and/or composition in the treatment of AHF as defined in any one of Claims 1-61.

70. An acylated ghrelin molecule, an acylated ghrelin molecule for a use, a use, a method, a composition, a composition for a use, a kit of parts, substantially as claimed herein with reference to the accompanying claims, description, examples and figures.