Claims

1. Use of a heterodimeric fusion in the manufacture of a medicament for treating a subject having heart failure, optionally heart failure with pulmonary hypertension, wherein a pharmaceutical composition comprising a pharmaceutically acceptable excipient and about 1 mg to about 30 mg of the heterodimeric fusion is to be administered to the subject; wherein the heterodimeric fusion comprises:

(i) a first heterodimerisation domain connected to at least one Relaxin A chain polypeptide or a variant thereof; and

(ii) a second heterodimerisation domain connected to at least one Relaxin B chain polypeptide or a variant thereof;

wherein the first heterodimerisation domain heterodimerises with the second heterodimerisation domain; and wherein the heterodimeric fusion has Relaxin activity.

2. The use of claim 1, wherein the amount of the heterodimeric fusion in the pharmaceutical composition is about 1 mg, about 1.1 mg, about 5.4 mg, or about 30 mg.

3. The use of claim 1, wherein the amount of the heterodimeric fusion in the pharmaceutical composition is about 1 mg or about 1.1 mg.

4. The use of claim 1, wherein the amount of the heterodimeric fusion in the pharmaceutical composition is about 5.4 mg.

5. The use of claim 1, wherein the amount of the heterodimeric fusion in the pharmaceutical composition is about 30 mg.

6. The use of any one of claims 1-5, wherein the pharmaceutical composition is to be administered to the subject biweekly.

7. The use of any one of claims 1-6, wherein the pharmaceutical composition is to be administered to the subject subcutaneously.

8. The use of any one of claims 1-7, wherein the subject has one or more of:

(a) New York Heart Association (NYHA) Functional Class II-IV;

(b) mean pulmonary arterial pressure (mPAP) greater than 20 mmHg; and

(c) pulmonary artery wedge pressure (PAWP) greater than 15 mmHg.

9. The use of any one of claims 1-8, wherein endogenous relaxin plasma levels in the subject are about 10,000-fold lower than relaxin plasma levels in pregnant subjects in their first trimester.

10. The use of any one of claims 1-9, wherein the amount of the heterodimeric fusion in the pharmaceutical composition is sufficient to provide the subject relaxin exposure that corresponds to up to about 0.5-fold, up to about 2.5-fold, or up to about 15-fold endogenous relaxin levels in the plasma of pregnant subjects in their first trimester.

11. The use of any one of claims 1-10, wherein administration of the pharmaceutical composition is sufficient to result in a plasma concentration of the heterodimeric fusion of 0.026 µg/mL to 1.6 µg/mL in the subject.

12. The use of any one of claims 1-11, wherein administration of the pharmaceutical composition is sufficient to result in a dose dependent increase in renin of at least 2-fold compared to baseline levels.

13. The use of any one of claims 1-12, wherein, following administration of the pharmaceutical composition, hematocrit levels in the subject are reduced by no more than 5-7 percent, e.g., by no more than 5 percent or no more than 7 percent, compared to baseline levels.

14. The use of any one of claims 1-13, wherein, following administration of the pharmaceutical composition, hemoglobin levels in the subject are reduced by no more than 3 percent or by no more than 5 percent compared to baseline levels.

15. The use of any one of claims 1-14, wherein albumin levels in the subject are not significantly decreased, compared to baseline levels, following administration of the pharmaceutical composition.

16. The use of any one of claims 1-15, wherein blood pressure (e.g. systolic blood pressure) of the subject is not significantly changed, compared to baseline blood pressure (e.g. systolic blood pressure), following administration of the pharmaceutical composition.

17. The use of any one of claims 1-16, wherein administration of the pharmaceutical composition is sufficient to result in one or more of:

(a) a reduction in pulmonary vascular resistance (PVR);

(b) reduction in a reduction in mean Pulmonary Artery Pressure (mPAP);

(c) a reduction in estimated Pulmonary Artery Diastolic Pressure (ePAD);

(d) an increase in stroke volume (SV);

(e) a decrease in systemic vascular resistance (SVR) and/or an increase in estimated glomerular filtration rate (eGFR);

(f) an increase in ejection fraction; and/or

(g) an increase in cardiac output;

as compared to baseline levels.

18. The use of any one of claims 1-17, wherein administration of the pharmaceutical composition is sufficient to result in an increase in stroke volume (SV) in the subject by at least about 1 percent, compared to baseline levels, optionally at a biweekly dose of about 1 mg or about 1.1 mg.

19. The use of any one of claims 1-18, wherein administration of the pharmaceutical composition is sufficient to result in an increase in SV in the subject by at least about 5-25 percent, compared to baseline levels, optionally at a biweekly dose of about 5.4 mg.

20. The use of any one of claims 1-19, wherein administration of the pharmaceutical composition is sufficient to result in an increase in SV in the subject by at least about 10-50 percent, compared to baseline levels, optionally at a biweekly dose of about 30 mg.

21. The use of any one of claims 1-20, wherein administration of the pharmaceutical composition is sufficient to result in a decrease in systemic vascular resistance (SVR) in the subject by at least about 8-20 percent, compared to baseline levels, optionally at a biweekly dose of about 1 mg or about 1.1 mg.

22. The use of any one of claims 1-21, wherein administration of the pharmaceutical composition is sufficient to result in a decrease in SVR in the subject by at least about 15-30 percent, compared to baseline levels, optionally at a biweekly dose of about 5.4 mg.

23. The use of any one of claims 1-22, wherein administration of the pharmaceutical composition is sufficient to result in a decrease in SVR in the subject by at least about 20-35 percent, compared to baseline levels, optionally at a biweekly dose of about 30 mg.

24. The use of any one of claims 17-23, wherein the change in PVR, mPAP, ePAD, SV, SVR, eGFR, ejection fraction and/or cardiac output is as measured after 1-24 weeks of treatment, optionally after 24 weeks of treatment.

25. The use of any one of claims 1-24, wherein the heterodimeric fusion agonizes the Relaxin family peptide receptor 1 (RXFP1).

26. The use of any one of claims 1-25, wherein the at least one Relaxin A chain polypeptide or variant thereof and the at least one Relaxin B chain polypeptide or variant thereof: (i) are covalently bound by at least one inter-chain disulphide bond; and/or (ii) are not covalently linked to each other by an amino acid linker.

27. The use of any one of claims 1-26, wherein the at least one Relaxin A chain polypeptide is a Relaxin-2 A chain polypeptide, and the at least one Relaxin B chain polypeptide is a Relaxin-2 B chain polypeptide.

28. The use of any one of claims 1-27, wherein the at least one Relaxin-2 A chain polypeptide comprises the amino acid sequence of SEQ ID NO: 1 and the at least one Relaxin-2 B chain polypeptide comprises the amino acids sequence of SEQ ID NO: 2.

29. The use of any one of claims 1-28, wherein the at least one Relaxin A chain polypeptide or variant thereof is connected to the first heterodimerisation domain via a connector and the at least one Relaxin B chain polypeptide or variant thereof is connected to the second heterodimerisation domain via a connector, optionally wherein one or optionally both connectors are polypeptides.

30. The use of any one of claims 26-29, wherein one or optionally both connectors have a length of between 6 and 40 amino acids, optionally a length of 21 amino acids.

31. The use of claim 30, wherein one or optionally both connectors are G4S/G5S amino acid linkers.

32. The use of claim 30 or claim 31, wherein one or optionally both connectors have the amino acid sequence of SEQ ID NO: 5.

33. The use of any one of claims 1-32, wherein the first heterodimerisation domain is derived from a first immunoglobulin Fc region and the second heterodimerisation domain is derived from a second immunoglobulin Fc region, wherein the first and second Fc regions comprise the constant domains CH2 and CH3, optionally CH2 and CH3 domains from an IgG1 immunoglobulin, further optionally wherein the CH2 and/or CH3 domains are mutated.

34. The use of claim 33, wherein the C-terminus of the first Fc region is connected to the N-terminus of the at least one Relaxin A chain polypeptide and the C-terminus of the second Fc region is connected to the N-terminus of the at least one Relaxin B chain polypeptide.

35. The use of claim 33 or claim 34, wherein the first and second Fc regions comprise heterodimerisation-promoting amino acid amino acid mutations, optionally wherein the heterodimerisation-promoting amino acid mutations are present in the CH3 domains.

36. The use of claim 35, wherein the heterodimerisation-promoting amino acid mutations in the first Fc region comprise S354C and T366W in the CH3 domain and the heterodimerisation-promoting amino acid mutations in the second Fc region comprise Y349C, T366S, L368A, and Y407V in the CH3 domain, wherein the amino acid numbering is according to the EU index as in Kabat.

37. The use of any one of claims 33-36, wherein the first and/or second Fc region further comprises the amino acid mutations L234F, L235E, and P331S, wherein the amino acid numbering is according to the EU index as in Kabat.

38. The use of any one of claims 33-37, wherein the first Fc region comprises the amino acid sequence of SEQ ID NO: 4 and the second Fc region comprises the amino acid sequence of SEQ ID NO: 3.

39. The use of any one of claims 27-38, wherein the heterodimeric fusion comprises the amino acid sequence of SEQ ID NO: 11 and the amino acid sequence of SEQ ID NO: 20.

40. The use of any one of claims 33-39, wherein the heterodimeric fusion further comprises a second Relaxin A chain polypeptide or variant thereof connected to the N-terminus of the first Fc region and a second Relaxin B chain polypeptide or variant thereof connected to the N-terminus of the second Fc region, optionally wherein the second Relaxin A chain is connected to the first Fc region via a connector polypeptide, optionally having the amino acid sequence of SEQ ID NO: 5, and the second Relaxin B chain is connected to the second Fc region via a connector polypeptide, optionally having the amino acid sequence of SEQ NO ID: 5.

41. The use of any one of claims 1-40, wherein the heterodimeric fusion comprises or consists of AZD3427.

42. The use of any one of claims 1-41, wherein the heterodimeric fusion is AZD3427 and is to be administered biweekly to the subject subcutaneously at a dose of about 1 mg or about 1.1 mg.

43. The use of any of one of claims 1-41, wherein the heterodimeric fusion is AZD3427 and is to be administered biweekly to the subject subcutaneously at a dose of about 5.4 mg.

44. The use of any one of claims 1-41, wherein the heterodimeric fusion is AZD3427 and is to be administered biweekly to the subject subcutaneously at a dose of about 30 mg.

45. Use of a heterodimeric fusion in the manufacture of a medicament for treating a subject having heart failure, optionally heart failure with pulmonary hypertension, wherein a pharmaceutical composition comprising a pharmaceutically acceptable excipient and about 1 mg to about 30 mg of the heterodimeric fusion is to be administered to the subject; wherein the heterodimeric fusion comprises:

(i) an FcX-con-A fusion polypeptide; and

(ii) an FcY-con-B fusion polypeptide,

wherein:

A is a Relaxin A chain or variant thereof, e.g., a Relaxin-2 A chain or variant thereof;

B is a Relaxin B chain or variant thereof, e.g., a Relaxin-2 B chain or variant thereof;

FcX is an Fc region comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin with amino acid mutations, optionally the amino acid mutations S354C and T366W;

FcY is an Fc region comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin comprising amino acid mutations, optionally the amino acid mutations Y349C, T366S, L368A, and Y407V; and

con is a connector polypeptide, optionally having the sequence SEQ ID NO: 5,

wherein the amino acid numbering is according to the EU index as in Kabat, wherein FcX heterodimerises with FcY, and wherein the heterodimeric fusion has Relaxin activity.

46. The use of claim 45, wherein the heterodimeric fusion comprises or consists of AZD3427.

47. The use of claim 45 or claim 46, wherein the amount of heterodimeric fusion in the pharmaceutical composition is about 1 mg, about 1.1 mg, about 5.4 mg, or about 30 mg.

48. The use of any one of claims 45-47, wherein the pharmaceutical composition is to be administered to the subject biweekly.

49. The use of any one of claims 45-48, wherein the pharmaceutical composition is to be administered to the subject subcutaneously.

50. The use of any one of the preceding claims, wherein the subject has heart failure with pulmonary hypertension Group 2.