~~Claims~~

CLAIMS

1. A combination comprising an FGF21 (fibroblast growth factor 21) compound and a GLP-1R (glucagon-like peptide-1 receptor) agonist,

wherein the FGF21 compound has an FGF21 activity which is the same as or ~~substantially~~is in the ~~same as~~range of 50% to 150% of the FGF21 activity of native FGF21, and

wherein the GLP-1R agonist has a GLP-1R agonistic activity which is 9- to 531-fold reduced as compared to the GLP-1R agonistic activity of native GLP-1(7-36~~).~~), wherein the GLP-1R agonist comprises or consists of the amino acid sequence

H-G-E-G-T-F-T-S-D-X_{10}-S-X_{12}-Q-X_{14}-X_{15}-E-E-X_{18}-V-X_{20}-X_{21}-F-I-E-W-L-X_{27}-X_{28}-X_{29}-X_{30}

(SEQ ID NO: 37),

wherein

X_{10} is L or K;

X_{12} is K or I;

X_{14} is L;

X_{15} is E or D;

X_{18} is A or R;

X_{20} is R or Q;

X_{21} is L or E;

X_{27} is L, E, K or V;

X_{28} is A;

X_{29} is T or G;

X_{30} is G or R;

wherein, optionally, the amino acid sequence comprises at least one additional amino acid residue at its N-terminus; and

wherein, optionally, the amino acid sequence comprises a peptide extension consisting of up to 12, 11 or 10 amino acid residues at its C-terminus.

2. The combination according to claim 1, wherein the GLP-1R agonist has a GLP-1R agonistic activity which is 9- to 482-fold or 9- to 319-fold or 9- to 121-fold reduced as compared to the GLP-1R agonistic activity of native GLP-1(7-36~~).~~

3. The combination according to claim 1,); or wherein the GLP-1R agonist has a GLP-1R agonistic activity which is 18- to 501-fold or 18- to 469-fold or 18- to 313-fold or 18- to 123-fold reduced as compared to the GLP-1R agonistic activity of native GLP-1(7-36).

43. The combination according to any of claimsclaim 1 to 3or 2, wherein the FGF21 compound is native FGF21 or an FGF21 variant having at least 80% or at least 90% or at least 95% amino acid sequence identity to the amino acid sequence of native FGF21.

54. The combination according to any of claims 1 to 4, wherein the GLP-1R agonist comprises or consists of the amino acid sequence

H-G-E-G-T-F-T-S-D-X_{10}-S-X_{12}-Q-X_{14}-X_{15}-E-E-X_{18}-V-X_{20}-X_{21}-F-I-E-W-L-X_{27}-X_{28}-X_{29}-X_{30} (SEQ ID NO: 37),

wherein

X_{10} is L or K;

X_{12} is K or I;

X_{14} is L or M;

X_{15} is E or D;

X_{18} is A or R;

X_{20} is R or Q;

X_{21} is L or E;

X_{27} is L, E, K or V;

X_{28} is A, N or K;

X_{29} is T or G;

X_{30} is G or R;

wherein, optionally, the amino acid sequence comprises at least one additional amino acid residue at its N-terminus; and

wherein, optionally, the amino acid sequence comprises a peptide extension consisting of up to 12, 11 or 10 amino acid residues at its C-terminus.

6. The combination according to any of claims 1 to 53, wherein the GLP-1R agonist comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 10, 12, 14, 15, 16, 17, 19 and 20.

~~7~~5. A pharmaceutical composition comprising an FGF21 (fibroblast growth factor 21) compound and a GLP-1R (glucagon-like peptide-1 receptor) agonist together with a pharmaceutically acceptable carrier and/or excipient,

wherein the FGF21 compound has an FGF21 activity which is the same as or ~~substantially~~is in the ~~same as~~range of 50% to 150% of the FGF21 activity of native FGF21, and

wherein the GLP-1R agonist has a GLP-1R agonistic activity which is 9- to 531-fold reduced as compared to the GLP-1R agonistic activity of native GLP-1(7-36~~).~~), wherein the GLP-1R agonist comprises or consists of the amino acid sequence

~~8~~ H-G-E-G-T-F-T-S-D-X_{10}-S-X_{12}-Q-X_{14}-X_{15}-E-E-X_{18}-V-X_{20}-X_{21}-F-I-E-W-L-X_{27}-X_{28}-X_{29}-X_{30} (SEQ ID NO: 37),

wherein

X_{10} is L or K;

X_{12} is K or I;

X_{14} is L;

X_{15} is E or D;

X_{18} is A or R;

X_{20} is R or Q;

X_{21} is L or E;

X_{27} is L, E, K or V;

X_{28} is A;

X_{29} is T or G;

X_{30} is G or R;

wherein, optionally, the amino acid sequence comprises at least one additional amino acid residue at its N-terminus; and

wherein, optionally, the amino acid sequence comprises a peptide extension consisting of up to 12, 11 or 10 amino acid residues at its C-terminus.

6. A fusion molecule comprising an FGF21 (fibroblast growth factor 21) compound and a GLP-1R (glucagon-like peptide-1 receptor) agonist,

wherein the FGF21 compound has an FGF21 activity which is the same as or ~~substantially~~is in the ~~same as~~range of 50% to 150% of the FGF21 activity of native FGF21, and

wherein the GLP-1R agonist has a GLP-1R agonistic activity which is 9- to 531-fold reduced as compared to the GLP-1R agonistic activity of native GLP-1(7-36~~).~~), wherein the GLP-1R agonist comprises or consists of the amino acid sequence

~~9~~H-G-E-G-T-F-T-S-D-X_{10}-S-X_{12}-Q-X_{14}-X_{15}-E-E-X_{18}-V-X_{20}-X_{21}-F-I-E-W-L-X_{27}-X_{28}-X_{29}-X_{30} (SEQ ID NO: 37),

wherein

X_{10} is L or K;

X_{12} is K or I;

X_{14} is L;

X_{15} is E or D;

X_{18} is A or R;

X_{20} is R or Q;

X_{21} is L or E;

X_{27} is L, E, K or V;

X_{28} is A;

X_{29} is T or G;

X_{30} is G or R;

wherein, optionally, the amino acid sequence comprises at least one additional amino acid residue at its N-terminus; and

wherein, optionally, the amino acid sequence comprises a peptide extension consisting of up to 12, 11 or 10 amino acid residues at its C-terminus.

7. The pharmaceutical composition according to claim ~~7~~5 or the fusion molecule according to claim ~~8~~6, wherein the GLP-1R agonist and/or the FGF21 compound are as defined in any of claims 2 to ~~6~~4.

~~10~~8. A nucleic acid molecule encoding a fusion molecule according to claim ~~8~~6 or ~~9~~7.

~~11~~9. A host cell containing a nucleic acid molecule according to claim 8.

10.

~~12.~~ A kit comprising a combination according to any of claims 1 to ~~6~~4, a pharmaceutical composition according to claim ~~7~~5 or ~~9~~7, a fusion molecule according to claim ~~8~~6 or ~~9~~7, a nucleic acid molecule according to claim ~~10~~8 or a host cell according to claim ~~11~~9.

~~13~~11. A combination according to any of claims 1 to ~~6~~4, a pharmaceutical composition according to claim ~~7~~5 or ~~9~~7, a fusion molecule according to claim ~~8~~6 or ~~9~~7, a nucleic acid molecule according to claim ~~10~~8 or a host cell according to claim ~~11~~9 for use as a medicament.

~~14~~12. A combination according to any of claims 1 to ~~6~~4, a pharmaceutical composition according to claim ~~7~~5 or ~~9~~7, a fusion molecule according to claim ~~8~~6 or ~~9~~7, a nucleic acid molecule according to claim ~~10~~8 or a host cell according to claim ~~11~~9 for use in the treatment of a disease or disorder selected from the group consisting of obesity~~, being overweight~~, metabolic syndrome, diabetes mellitus, diabetic retinopathy, hyperglycemia, dyslipidemia, Non-Alcoholic SteatoHepatitis (NASH) and atherosclerosis.

~~15. Use of a combination according to any of claims 1 to 6, a pharmaceutical composition according to claim 7 or 9, a fusion molecule according to claim 8 or 9, a nucleic acid molecule according to claim 10 or a host cell according to claim 11 in the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of obesity, being overweight, metabolic syndrome, diabetes mellitus, diabetic retinopathy, hyperglycemia, dyslipidemia, Non-Alcoholic SteatoHepatitis (NASH) and atherosclerosis.~~

~~16. A method of treating a disease or disorder selected from the group consisting of obesity, being overweight, metabolic syndrome, diabetes mellitus, diabetic retinopathy, hyperglycemia, dyslipidemia, Non-Alcoholic SteatoHepatitis (NASH) and atherosclerosis, the method comprising administering a combination according to any of claims 1 to 6, a pharmaceutical composition according to claim 7 or 9, a fusion molecule according to claim 8 or 9, a nucleic acid molecule according to claim 10 or a host cell according to claim 11 to a subject in need thereof.~~

~~17~~13. The combination, pharmaceutical composition, fusion molecule, nucleic acid molecule or host cell for use according to claim ~~14, the use of claim 15 or the method of claim 16~~12, wherein the diabetes mellitus is type 1 diabetes mellitus or type 2 diabetes mellitus.

~~18~~14. A GLP-1R agonist having a GLP-1R agonistic activity which is 9- to 531-fold reduced as compared to the GLP-1R agonistic activity of native GLP-1(7-36~~).~~), wherein the GLP-1R agonist comprises or consists of the amino acid sequence

~~19. The GLP-1R agonist according to claim 18 comprising or consisting of the amino acid sequence~~

H-G-E-G-T-F-T-S-D-X_{10}-S-X_{12}-Q-X_{14}-X_{15}-E-E-X_{18}-V-X_{20}-X_{21}-F-I-E-W-L-X_{27}-X_{28}-X_{29}-X_{30}
(SEQ ID NO:37),

wherein

X_{10} is L or K;

X_{12} is K or I;

X_{14} is L~~ or M~~;

X_{15} is E or D;

X_{18} is A or R;

X_{20} is R or Q;

X_{21} is L or E;

X_{27} is L, E, K or V;

X_{28} is A~~, N or K~~;

X_{29} is T or G;

X_{30} is G or R;

wherein, optionally, the amino acid sequence comprises at least one additional amino acid residue at its N-terminus; and

wherein, optionally, the amino acid sequence comprises a peptide extension consisting of up to 12, 11 or 10 amino acid residues at its C-terminus.

~~20~~15. The GLP-1R agonist according to claim ~~18 or 19~~14 comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 10, 12, 14, ~~15,~~ 16, 17, 19 and 20.