

Claims

- 5 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 or substantially the same
as 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
10 compared to the GLP-1R agonistic activity of native GLP-1(7-36).
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).
- 15 3. The combination according to claim 1, 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).
- 20 4. The combination according to any of claims 1 to 3, 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.
5. The combination according to any of claims 1 to 4, wherein the GLP-1R agonist
25 comprises or consists of the amino acid sequence

H-G-E-G-T-F-T-S-D-X₁₀-S-X₁₂-Q-X₁₄-X₁₅-E-E-X₁₈-V-X₂₀-X₂₁-F-I-E-W-L-X₂₇-X₂₈-X₂₉-X₃₀ (SEQ ID
NO: 37),

- 30 wherein
- X₁₀ is L or K;
X₁₂ is K or I;
X₁₄ is L or M;
X₁₅ is E or D;
- 35 X₁₈ is A or R;
X₂₀ is R or Q;
X₂₁ is L or E;
X₂₇ is L, E, K or V;

X₂₈ is A, N or K;

X₂₉ is T or G;

X₃₀ is G or R;

wherein, optionally, the amino acid sequence comprises at least one additional amino acid
5 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 5, wherein the GLP-1R agonist comprises
10 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. A pharmaceutical composition comprising an FGF21 (fibroblast growth factor 21)
compound and a GLP-1R (glucagon-like peptide-1 receptor) agonist together with a
15 pharmaceutically acceptable carrier and/or excipient,
wherein the FGF21 compound has an FGF21 activity which is the same or substantially the same
as 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).

20 8. 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 or substantially the same
as the FGF21 activity of native FGF21, and
25 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).

9. The pharmaceutical composition according to claim 7 or the fusion molecule according to
claim 8, wherein the GLP-1R agonist and/or the FGF21 compound are as defined in any of claims
30 2 to 6.

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

11. A host cell containing a nucleic acid molecule according to claim 10.

35 12. A kit comprising 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.

13. 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 for use as a medicament.
- 5
14. 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 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.
- 10
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.
- 15
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.
- 20
- 25
17. 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, wherein the diabetes mellitus is type 1 diabetes mellitus or type 2 diabetes mellitus.
- 30
18. 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).
19. The GLP-1R agonist according to claim 18 comprising or consisting of the amino acid sequence
- 35
- H-G-E-G-T-F-T-S-D-X₁₀-S-X₁₂-Q-X₁₄-X₁₅-E-E-X₁₈-V-X₂₀-X₂₁-F-I-E-W-L-X₂₇-X₂₈-X₂₉-X₃₀ (SEQ ID NO:37),

wherein

X₁₀ is L or K;

X₁₂ is K or I;

5 X₁₄ is L or M;

X₁₅ is E or D;

X₁₈ is A or R;

X₂₀ is R or Q;

X₂₁ is L or E;

10 X₂₇ is L, E, K or V;

X₂₈ is A, N or K;

X₂₉ is T or G;

X₃₀ is G or R;

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