CLAIMS

1. A GLP-1 receptor-amylin receptor co-agonist comprising a polypeptide (R1) according to Formula I:

Z1-Z2-Z3,

comprising 1-3 lysine (Lys, K) residues and no disulfide bridge; wherein:

- Z1 is a GLP-1 receptor agonist peptide comprising a maximum of 9 amino acid modifications relative to SEQ ID NO: 1, with the proviso that Z1 does not comprise an isoleucine (Ile, I) at position 22;
- Z2 is an optional peptide linker;
- Z3 is an amylin receptor agonist peptide comprising a C-terminal amide and a maximum of 7 amino acid modifications relative to SEQ ID NO: 79, with the proviso that Z3 does not comprise a proline (Pro, P) at position 12;

and further comprising 1-3 protraction moieties (R2-R3), attached to the polypeptide (R1) via said 1-3 lysine (Lys, K) residues.

2. The GLP-1 receptor-amylin receptor co-agonist according to claim 1, wherein the GLP-1 receptor agonist peptide (Z1) comprises 0-3 lysine (Lys, K) residues at any one, or combination of, positions 9, 10, 12, 16, 19, 20, 21, 24, 25, 28, 29, 30 and/or 31, relative to SEQ ID NO: 238 or 255.

3. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the GLP-1 receptor agonist peptide (Z1) comprises 2 lysine (Lys, K) residues at positions:

- 12 and either 21, 30 or 31, or
- 21 and either 30 or 31;

preferably, at positions

- 12 and either 21 or 31, or
- 21 and 31,

relative to SEQ ID NO: 238 or 255.

4. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the GLP-1 receptor agonist peptide (Z1) comprises 1 lysine residue (Lys, K) at any one of positions 12, 20, 21, 28, 30 or 31; preferably, 1 lysine (Lys, K) residue at position 31.

5. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the peptide linker (Z2) comprises 0-3 lysine (Lys, K) residues; such as 1-2 lysine (Lys, K) residues; preferably, 1 lysine (Lys, K) residue.

6. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, wherein the amylin receptor agonist peptide (Z3) comprises 0-3 lysine (Lys, K) residues at any one of positions 1, 2, 3, 7, 14, 18, 20, 23 and/or 29, relative to SEQ ID NO: 240 or SEQ ID NO: 256; preferably, 1 lysine (Lys, K) residue at any one of positions 14, 18, 20, 23, 29; even more preferably, 1 lysine (Lys, K) residue at position 18.

7. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, comprising a GLP-1 receptor agonist peptide (Z1) according to Formula II (SEQ ID NO: 255):

Xaa1-Xaa2-Glu-Gly-Thr-Phe-Thr-Ser-Xaa9-Xaa10-Ser-Xaa12-Tyr-Leu-Glu-Xaa16-Xaa17-Ala-Xaa19-Xaa20-Xaa21-Phe-Ile-Xaa24-Xaa25-Leu-Val-Xaa28-Xaa29-Xaa30-Xaa31;

wherein

Xaa1 is His (H) or Imp,
Xaa2 is Aib, Ala (A), Gly (G) or Trp (W),
Xaa9 is Asp (D) or Lys (K),
Xaa10 is Lys (K) or Val (V),
Xaa12 is Lys (K), Arg (R) or Ser (S),
Xaa16 is Glu (E), Gly (G) or Lys (K),
Xaa17 is Gln (Q) or Lys (K),
Xaa19 is Ala (A) or Val (V),
Xaa20 is Lys (K) or Arg (R),
Xaa21 is Glu (E) or Lys (K),
Xaa24 is Ala (A), Glu (E),
Xaa25 is Lys (K) or Trp (W),
Xaa28 is Lys (K) or Arg (R),
Xaa29 is Lys (K) or Gly (G),
Xaa30 is Ala (A), Gly (G), Lys (K), Arg (R) or absent,
Xaa31 is Ala (A), Lys (K), Gly (G), Gln (Q) or absent.

8. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, comprising an amylin receptor agonist peptide (Z3) according to Formula III (SEQ ID NO: 256):

Xaa1-Xaa2-Xaa3-Leu-Ser-Thr-Xaa7-Ala-Leu-Gly-Arg-Leu-Ser-Xaa14-Glu-Leu-His-Xaa18-Leu-Xaa20-Thr-Leu-Xaa23-Arg-Thr-Glu-Thr-Gly-Xaa29-Gly-Ser-Pro,

wherein:

Xaa1 is Ala (A) or is absent,
Xaa2 is Lys (K) or Ser (S),
Xaa3 is Glu (E) or Arg (R),
Xaa7 is Ala (A) or Glu (E),
Xaa14 is Ala (A), or Lys (K),
Xaa18 is Glu (E), Lys (K) or Gln (Q),
Xaa20 is Ala (A), or Lys (K),
Xaa23 is Lys (K) or Pro (P),
Xaa29 is Ser (S) or Lys (K).

9. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, comprising:

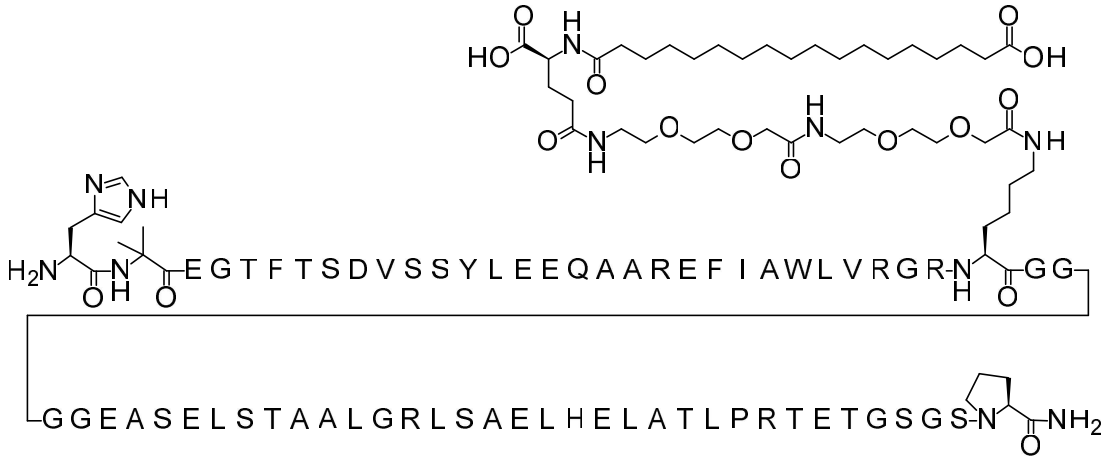
- one to two C14-C20 diacids; more preferably, one C16-C20 diacid or two C14-C18 diacids; even more preferably, a single C18 diacid; or
- 1-2 protractors selected from the group presented in Table 2.

10. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, comprising a polypeptide represented by any one of SEQ ID NOs 117-236; preferably, the polypeptide represented by SEQ ID NO: 153.

11. The GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims, which is any one of the compounds listed in Example 1a; preferably, any one of the compounds listed in Table 5.

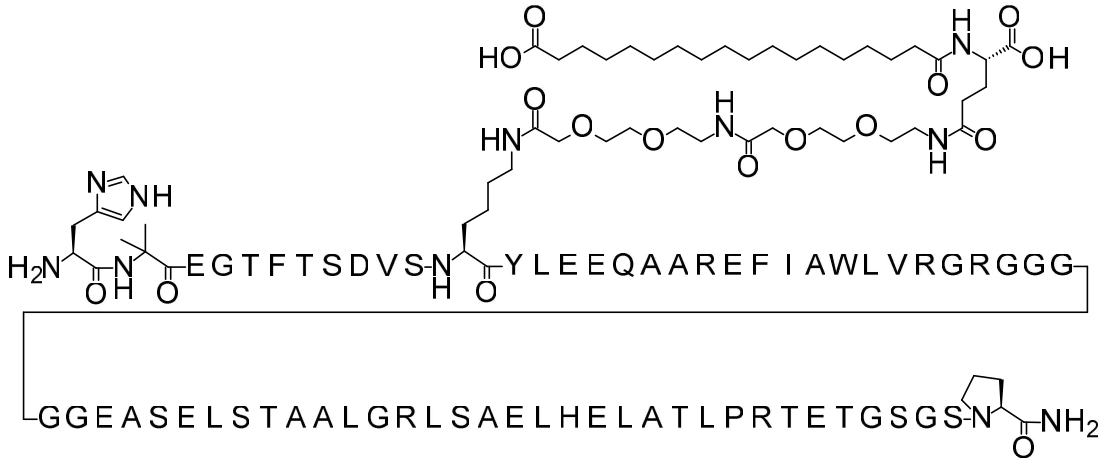
12. A GLP-1 receptor-amylin receptor co-agonist, which is H-Aib-EGTFTSDVSSYLEEQAAREFIAWLVRGR-K([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]ace

tyl])-GGGGEASELSTAALGRLSAELHELATLPRTETGSGSP-amide:



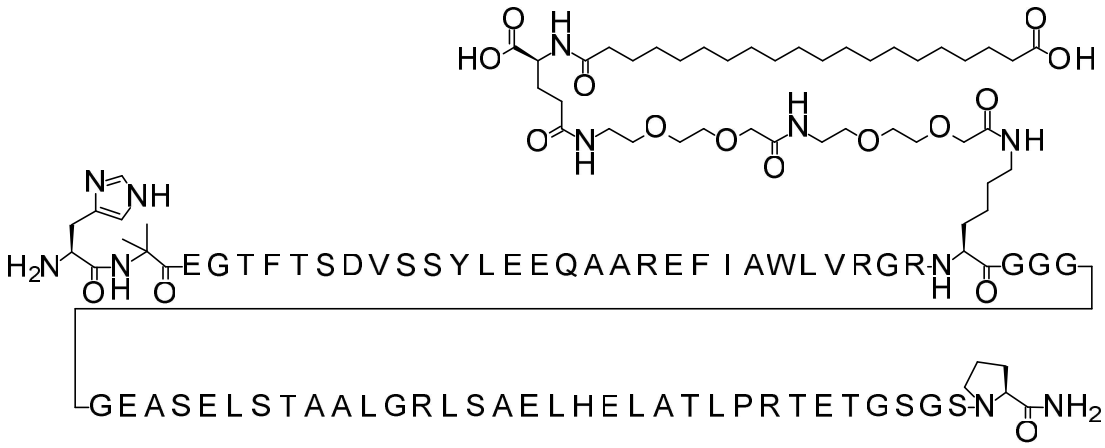
or

H-Aib-EGTFTSDVS-K([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl])-YLEEQAAREFIAWLVRGRGGGGGEASELSTAALGRLSAELHELATLPRTETGSGSP-amide:



or

H-Aib-EGTFTSDVSSYLEEQAAREFIAWLVRGR-K([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(19-carboxynonadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl])-GGGGEASELSTAALGRLSAELHELATLPRTETGSGSP-amide:



13. A pharmaceutical formulation comprising a GLP-1 receptor-amylin receptor co-agonist according to any one of the preceding claims.

~~14. The GLP-1 receptor-amylin receptor co-agonist according to any one of claims 1-12, or the pharmaceutical formulation according to claim 13, for use as a medicament.~~

~~15.~~14. ~~The~~ Use of the GLP-1 receptor-amylin receptor co-agonist according to any one of claims 1-12, or the pharmaceutical formulation according to claim 13, ~~for use~~ in the manufacture of a medicament for the treatment of a subject~~s~~ with any one or more of~~:~~;

a) an initial body mass index (BMI) of 27 or more, such as 30 or more, optionally in the presence of at least one weight-related comorbidity;

b) diabetes, optionally in the presence of at least one weight-related comorbidity;

c) cardiovascular disease~~,~~;

d) non-alcoholic steatohepatitis; and/or

e) cognitive impairment, such as that caused by Alzheimer's disease.

15. The use according to claim 14 for the treatment of a subject with an initial body mass index (BMI) of 27 or more, or the treatment of a subject with diabetes.