

It is, however, generally understood that GLP-1 lowers glucagon concentrations, has beneficial effects on inhibition of fast bowel movements (Tolessa et al., 1998, Dig. Dis. Sci. 43(10): 2284-90), and slows gastric emptying.

- 5 WO2013/164484 discloses GLP-2 analogues which comprise one or more substitutions compared to h[Gly2]GLP-2 and which may have the property of an altered GLP-1 activity, and their medical use.

- 10 WO2016/066818 describes peptides having dual agonist activity at the GLP-1 and GLP-2 receptors, and proposes medical uses thereof. However, there remains a need for further compounds which combine effective agonist activities at both receptors with acceptable levels of stability.

Summary

- 15 Broadly, the present disclosure relates to compounds which have agonist activity at the GLP-1 (glucagon-like peptide 1) and GLP-2 (glucagon-like peptide 2) receptors, e.g. as assessed in *in vitro* potency assays. Such compounds are referred to in this specification as “GLP-1/GLP-2 dual agonists”, or simply “dual agonists”. Thus, the compounds of the present disclosure have activities of both GLP-1 (7-36) and GLP-2
20 (1-33).

In one aspect, the present disclosure refers to a GLP-1/GLP-2 dual agonist represented by the formula:

R1-X*-U-R2

wherein:

- 25 R1 is hydrogen (Hy), C1-4 alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl, preferably R1 is Hy;

R2 is NH₂ or OH, preferably R2 is OH;

X* is a peptide of formula I:

- 30 H-X2-EG-X5-F-X7-X8-E-X10-X11-TIL-X15-X16-X17-A-X19-X20-X21-FI-X24-WL-X27-X28-X29-KIT-X33 (I)

wherein:

X2 is Aib or G;

- X5 is T or S;
- X7 is T or S;
- X8 is S, E or D;
- X10 is L, M, V or Ψ ;
- 5 X11 is A, N or S;
- X15 is D or E;
- X16 is G, E, A or Ψ ;
- X17 is Q, E, K, L or Ψ ;
- X19 is A, V or S;
- 10 X20 is R, K or Ψ ;
- X21 is D, L or E;
- X24 is A, N or S;
- X27 is I, Q, K, H or Y;
- X28 is Q, E, A, H, Y, L, K, R or S;
- 15 X29 is H, Y, K or Q;
- X33 is D or E;
- U is absent or a sequence of 1-15 residues each independently selected from K, k, E, A, T, I, L and Ψ ;
- the molecule contains one and only one Ψ , wherein Ψ is a residue of K, k, R, Orn,
- 20 Dap or Dab in which the side chain is conjugated to a substituent having the formula Z1- or Z1 Z2-, wherein:
- Z1- is CH₃-(CH₂)₁₀₋₂₂-(CO)- or HOOC-(CH₂)₁₀₋₂₂-(CO)-; and
- Z2- is selected from -ZS1-, -ZS1-ZS2-, -ZS2-ZS1-, -ZS2-, -ZS3-, -ZS1ZS3-, -ZS2ZS3-, -ZS3ZS1-, -ZS3ZS2-, -ZS1ZS2ZS3-, -ZS1ZS3ZS2-, -ZS2ZS1ZS3-, -ZS2ZS3ZS1-, -ZS3ZS1ZS2-, -ZS3ZS2ZS1-, ZS2ZS3ZS2-, wherein:
- 25 ZS1 is isoGlu, β -Ala, isoLys, or 4-aminobutanoyl;
- ZS2 is -(Peg3)_m- where m is 1, 2, or 3; and
- ZS3- is a peptide sequence of 1-6 amino acid units independently selected from the group consisting of A, L, S, T, Y, Q, D, E, K, k, R, H, F and G;

and wherein at least one of X5 and X7 is T;

or a pharmaceutically acceptable salt or solvate thereof.

In another aspect, the present disclosure refers to a dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 1 wherein X* is a peptide of

5 formula II:

H-X2-EG-X5-F-X7-SELATILD-X16-X17-AAR-X21-FIAWLI-X28-X29-KITD (II)

wherein:

X2 is Aib or G;

X5 is T or S;

10 X7 is T or S;

X16 is G or Ψ ;

X17 is Q, E, K, L or Ψ ;

X21 is D or L;

X28 is Q, E, A, H, Y, L, K, R or S; and

15 X29 is H, Y or Q.

In yet another aspect, the disclosure refers to a composition comprising a dual agonist according to the present disclosure, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier,

optionally wherein the carrier is a pharmaceutically acceptable carrier.

20 In yet another aspect, the present disclosure refers to a dual agonist according to the present disclosure, or a composition according to the present disclosure, for use in therapy.

In a first example there is provided a GLP-1/GLP-2 dual agonist represented by the

25 formula:

$R^1-X^*-U-R^2$

wherein:

R^1 is hydrogen (Hy), C_{1-4} alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is NH_2 or OH;

30 X* is a peptide of formula I:

H-X2-EG-X5-F-X7-X8-E-X10-X11-TIL-X15-X16-X17-A-X19-X20-X21-FI-X24-WL-X27-X28-X29-KIT-X33 (I)

wherein:

X2 is Aib or G

X5 is T or S;

X7 is T or S;

X8 is S, E or D;

Dual agonists having aspartic acid (Asp, D) at position 3 and glycine (Gly) in position 4 can be very potent agonists at the GLP-1 and GLP-2 receptors. However, this combination of substitutions results in compounds which are unstable and may not be suitable for long term storage in aqueous solution. Without wishing to be bound by theory, it is believed that the Asp at position 3 may isomerise to iso-Asp via a cyclic intermediate formed between the carboxylic acid functional group of its side chain and the backbone nitrogen atom of the residue at position 4.

It has now been found that molecules having glutamic acid (Glu, E) at position 3 instead of Asp are much less susceptible to such reactions and hence may be considerably more stable when stored in aqueous solution. However, replacement of Asp with Glu at position 3 in molecules having a lipophilic substituent in the middle portion of the peptide (e.g. at or near to positions 16 and 17) tends to reduce the potency at one or both of the GLP-2 receptor and the GLP-1 receptor, even though Glu is present at position 3 of the native GLP-1 molecule. Simultaneously incorporating a Thr residue at one or both of positions 5 and 7 appears to compensate for some or all of the lost potency. It is believed that further improvements in potency are also provided by incorporation of His (H), Tyr (Y), Lys (K) or Gln (Q) at position 29 instead of the Gly (G) and Thr (T) residues present in wild type human GLP-1 and 2 respectively.

In some examples of formula I:

- X2 is Aib or G
- X5 is T or S;
- X7 is T or S;
- 25 X8 is S;
- X10 is L or Ψ ;
- X11 is A or S;
- X15 is D or E;
- X16 is G, E, A or Ψ ;
- 30 X17 is Q, E, K, L or Ψ ;
- X19 is A or S;
- X20 is R or Ψ ;
- X21 is D, L or E;
- X24 is A;
- 35 X27 is I, Q, K, or Y;

X28 is Q, E, A, H, Y, L, K, R or S;

X29 is H, Y or Q; and

X33 is D or E.

- 5 Where Ψ is not at X16 or X17, it may be desirable that X16 is E and X17 is Q.
In some examples, X11 is A and X15 is D. In other examples, X11 is S and X15 is E.
In further examples, X11 is A and X15 is E.

In some examples, X27 is I.

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In some examples, X29 is H. In certain of these examples, X28 is A and X29 is H, or
X28 is E and X29 is H.

In some examples, X29 is Q and optionally X27 is Q.

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In some examples, the residues at X27-X29 have a sequence selected from:

IQH;

IEH

IAH;

20

IHH;

IYH;

ILH;

IKH;

IRH;

25

ISH;

QQH;

YQH;

KQH;

IQQ;

30

IQY;

IQT; and

IAY.

In some examples, X* is a peptide of formula II:

35 H-X2-EG-X5-F-X7-SELATILD-X16-X17-AAR-X21-FIAWLI-X28-X29-KITD (II)

wherein:

- X2 is Aib or G
X5 is T or S;
X7 is T or S;
X16 is G or Ψ ;
- 5 X17 is Q, E, K, L or Ψ ;
X21 is D or L;
X28 is Q, E, A, H, Y, L, K, R or S;
X29 is H, Y or Q;
- 10 In some examples of Formula I or Formula II, X16 is Ψ and X17 is Q, E, K or L. For example, X17 may be Q, or X17 may be selected from E, K and L. In other examples, X16 is G and X17 is Ψ .
- It may be desirable that X21 is D.
- 15 X28 may be selected from Q, E and A, e.g. it may be Q or E. In some residue combinations, Q may be preferred. In others, E may be preferred, including but not limited to when X16 is G and X17 is Ψ . Alternatively, X28 may be selected from A, H, Y, L, K, R and S.
- 20 X* may be a peptide of formula III:
H[Aib]EG-X5-F-X7-SE-X10-ATILD-X16-X17-AA-X20-X21-FIAWLI-X28-X29-KITD (III)
wherein:
X5 is T or S;
- 25 X7 is T or S;
X10 is L or Ψ ;
X16 is G, E, A or Ψ ;
X17 is Q, E, K, L or Ψ ;
X20 is R or Ψ ;
- 30 X21 is D or L;
X28 is E, A or Q;
X29 is H, Y or Q;
and at least one of X5 and X7 is T.
- 35 X* may be a peptide of formula IV:
H[Aib]EG-X5-F-X7-SELATILD-X16-X17-AAR-X21-FIAWLI-X28-X29-KITD (IV)
wherein:

- X5 is T or S;
 X7 is T or S;
 X16 is G or Ψ ;
 X17 is E, K, L or Ψ ;
- 5 X21 is D or L;
 X28 is E or A;
 X29 is H, Y or Q;
 and at least one of X5 and X7 is T.
- 10 In some examples of any of formulae I to IV, X16 is Ψ and X17 is E, K or L.

In other examples of formula I to IV, X16 is G and X17 is Ψ .

In either case, the following combinations of residues may also be included:

- 15 X21 is D and X28 is E;
 X21 is D and X28 is A;
 X21 is L and X28 is E;
 X21 is L and X28 is A.
- 20 X* may be a peptide of formula V:
 H[Aib]EG-X5-F-X7-SELATILD- Ψ -QAARDFIAWLI-X28-X29-KITD (V)
 wherein
 X5 is T or S;
 X7 is T or S;
- 25 X28 is Q, E, A, H, Y, L, K, R or S, , e.g. Q, E, A, H, Y or L;
 X29 is H, Y or Q;
 and at least one of X5 and X7 is T.

- In some examples of formula III, X28 is Q or E. In some examples of formula III, X28
 30 is Q. In other examples, X28 is A, H, Y, L, K, R or S, e.g. A, H, Y or L.

In any of the formulae or examples described above, the dual agonist contains one of the following combinations of residues:

- X5 is S and X7 is T;
- 35 X5 is T and X7 is S;

X5 is T and X7 is T.

It may be preferred that X5 is S and X7 is T, or X5 is T and X7 is T.

- 5 In any of the formulae or examples described above, it may be desirable that X29 is H.

In some examples, Ψ is a Lys residue whose side chain is conjugated to the substituent Z^1 - or Z^1 - Z^2 -.

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In some examples, Z^1 -, alone or in combination with $-Z^2$ -, is dodecanoyl, tetradecanoyl, hexadecanoyl, octadecanoyl or eicosanoyl.

In some examples, Z^1 -, alone or in combination with $-Z^2$ -, is:

- 15 13-carboxytridecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{12}-(\text{CO})-$;
15-carboxypentadecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{14}-(\text{CO})-$;
17-carboxyheptadecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{16}-(\text{CO})-$;
19-carboxynonadecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{18}-(\text{CO})-$; or
21-carboxyheneicosanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{20}-(\text{CO})-$.

20

In some examples Z^2 is absent.

In some examples, Z^2 comprises Z^{S1} alone or in combination with Z^{S2} and/or Z^{S3} .

- 25 In such examples:

$-Z^{S1}$ - is isoGlu, β -Ala, isoLys, or 4-aminobutanoyl;

$-Z^{S2}$ -, when present, is $-(\text{Peg}3)_m$ - where m is 1, 2, or 3; and

$-Z^{S3}$ - is a peptide sequence of 1-6 amino acid units independently selected from the group consisting of A, L, S, T, Y, Q, D, E, K, k, R, H, F and G, such as the peptide

- 30 sequence KEK.

Z^2 may have the formula $-Z^{S1}-Z^{S3}-Z^{S2}$ -, where Z^{S1} is bonded to Z^1 and Z^{S2} is bonded to the side chain of the amino acid component of Ψ .

- 35 Thus, in some examples, $-Z^2$ - is:

isoGlu(Peg 3)₀₋₃;

β -Ala(Peg 3)₀₋₃;

isoLys(Peg3)₀₋₃; or
4-aminobutanoyl(Peg3)₀₋₃.

In further examples, -Z²- is:

5 isoGlu-KEK-(Peg3)₀₋₃.

Specific examples of the substituent Z¹-Z²- are set out below. In some examples, Z¹-Z²- is [17-carboxy-heptadecanoyl]-isoGlu. For example, Ψ may be K([17-carboxy-heptadecanoyl]-isoGlu). In some examples, Z¹-Z²- is:

- 10 [17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3-;
[17-carboxy-heptadecanoyl]-isoGlu-Peg3-;
[19-Carboxy-nonadecanoyl]-isoGlu-;
[19-Carboxy-nonadecanoyl]-isoGlu-KEK-;
[19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3-;
15 [19-carboxy-nonadecanoyl]-isoGlu-KEK-Peg3-Peg3-;
[19-carboxy-nonadecanoyl]-isoGlu-Peg3-Peg3-;
[19-carboxy-nonadecanoyl]-isoLys-Peg3-Peg3-Peg3-;
[Hexadecanoyl]-βAla-;
[Hexadecanoyl]-isoGlu-; or
20 Octadecanoyl-.

For example, Ψ may be:

- K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3);
K([17-carboxy-heptadecanoyl]-isoGlu-Peg3);
25 K([19-Carboxy-nonadecanoyl]-isoGlu);
K([19-Carboxy-nonadecanoyl]-isoGlu-KEK);
K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3);
K([19-carboxy-nonadecanoyl]-isoGlu-KEK-Peg3-Peg3);
K([19-carboxy-nonadecanoyl]-isoGlu-Peg3-Peg3);
30 K([19-carboxy-nonadecanoyl]-isoLys-Peg3-Peg3-Peg3);
K([Hexadecanoyl]-βAla-;
K([Hexadecanoyl]-isoGlu); or
K(Octadecanoyl).

- 35 When present, U represents a peptide sequence of 1-15 residues each independently selected from K (i.e. L-lysine), k (i.e. D-lysine) E (Glu), A (Ala), T (Thr), I (Ile), L (Leu)

and Ψ . For example, U may be 1-10 amino acids in length, 1-7 amino acids in length, 3-7 amino acids in length, 1-6 amino acids in length, or 3-6 amino acids in length.

Typically U includes at least one charged amino acid (K, k or E) and preferably two or more charged amino acids. In some examples it includes at least 2 positively charged amino acids (K or k), or at least 1 positively charged amino acid (K or k) and at least one negatively charged amino acid (E). In some examples, all amino acid residues of U (except for ψ , if present) are charged. For example, U may be a chain of alternately positively and negatively charged amino acids.

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In certain examples, U comprises residues selected only from K, k, E and Ψ .

In certain examples, U comprises residues selected only from K, k, and Ψ .

15 When U comprises only lysine residues (whether K or k), all residues may have an L-configuration or all may have a D-configuration. Examples include K_{1-15} , K_{1-10} and K_{1-7} , e.g., K_3 , K_4 , K_5 , K_6 and K_7 , especially K_5 and K_6 . Further examples include k_{1-15} , k_{1-10} and k_{1-7} , e.g. k_3 , k_4 , k_5 , k_6 and k_7 , especially k_5 and k_6 .

20 Further examples of peptide sequences U include KEK, EKEKEK, EkEkEk, AKAAEK, AKEKEK and ATILEK.

In any case, one of those residues may be exchanged for Ψ . Where the sequence U contains a residue Ψ , it may be desirable that the C-terminal residue of U is Ψ . Thus, further examples of sequences U include $K_{1-14}\text{-}\Psi$, $K_{1-9}\text{-}\Psi$ and $K_{1-6}\text{-}\Psi$, e.g., $K_2\text{-}\Psi$, $K_3\text{-}\Psi$, $K_4\text{-}\Psi$, $K_5\text{-}\Psi$ and $K_6\text{-}\Psi$, especially $K_4\text{-}\Psi$ and $K_5\text{-}\Psi$. Yet further examples include $k_{1-14}\text{-}\Psi$, $k_{1-9}\text{-}\Psi$, and $k_{1-6}\text{-}\Psi$, e.g. $k_2\text{-}\Psi$, $k_3\text{-}\Psi$, $k_4\text{-}\Psi$, $k_5\text{-}\Psi$ and $k_6\text{-}\Psi$ especially $k_4\text{-}\Psi$ and $k_5\text{-}\Psi$. Yet further examples include KE Ψ , EKEKE Ψ , EkEkE Ψ AKAAE Ψ , AKEKE Ψ and ATILE Ψ .

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In some examples, U is absent.

In some examples, R^1 is Hy and/or R^2 is OH.

The peptide X^* or the peptide $X^*\text{-U}$ may have the sequence:

H[Aib]EGTFSSELATILD Ψ EAARDFIAWLIEHKITD;

Hy-H[Aib]EGTFSSELATILD[K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 47);
 Hy-H[Aib]EGTFSSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 48);
 Hy-H[Aib]EGTFSSELATILD[K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 49);
 Hy-H[Aib]EGTFSSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 50);
 Hy-H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK)]QAARDFIAWLIQHKITD-OH (Compound 51);
 Hy-H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 52);
 Hy-H[Aib]EGSFTSE[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]ATILDEQAARDFIAWLIQHKITD-OH (Compound 53);
 Hy-H[Aib]EGTFTSE[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]ATILDEQAARDFIAWLIQHKITD-OH (Compound 54);
 Hy-H[Aib]EGSFTSE[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]ATILDEQAARDFIAWLIQHKITD-OH (Compound 55);
 Hy-H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 56);
 Hy-H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 57);
 Hy-H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 58);
 Hy-H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]KAARDFIAWLIQHKITD-OH (Compound 59);
 Hy-H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 60);
 Hy-H[Aib]EGSFTSELATILEG[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]AARDFIAWLIQHKITD-OH (Compound 61);
 Hy-H[Aib]EGSFTSELATILDA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]AARDFIAWLIQHKITD-OH (Compound 62);
 Hy-H[Aib]EGSFTSELATILDA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]AARDFIAWLIQHKITD-OH (Compound 63);
 Hy-H[Aib]EGSFTSELATILDEQAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIQHKITD-OH (Compound 64);
 Hy-H[Aib]EGTFTSELATILDEQAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIQHKITD-OH (Compound 65);
 Hy-H[Aib]EGSFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]DFIAWLIQHKITD-OH (Compound 66);
 Hy-H[Aib]EGTFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]DFIAWLIQHKITD-OH (Compound 67); or
 Hy-H[Aib]EGSFTSELATILDAKAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIQHKITD-OH (Compound 68).

The dual agonist may be in the form of a pharmaceutically acceptable salt or solvate, such as a pharmaceutically acceptable acid addition salt.

- 5 The disclosure also provides a composition comprising a dual agonist of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, together with a carrier, excipient or vehicle. The carrier may be a pharmaceutically acceptable carrier.

The composition may be a pharmaceutical composition. The pharmaceutical composition may be formulated as a liquid suitable for administration by injection or infusion. It may be formulated to achieve slow release of the dual agonist.

- 5 The present disclosure further provides a dual agonist of the disclosure for use in therapy. In yet another example there is provided a dual agonist of the present disclosure for use as a medicament. Also provided is a dual agonist of the disclosure for use in a method of medical treatment.
- 10 The disclosure also provides a dual agonist of the disclosure for use in a method of increasing intestinal mass, improving intestinal function (especially intestinal barrier function), increasing intestinal blood flow, or repairing intestinal damage or dysfunction, e.g. damage to the intestinal epithelium.
- 15 The disclosure also provides a dual agonist of the disclosure for use in a method of prophylaxis or treatment of malabsorption, ulcers (e.g. peptic ulcers, Zollinger-Ellison Syndrome, drug-induced ulcers, and ulcers related to infections or other pathogens), short-bowel syndrome, cul-de-sac syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome (IBS), pouchitis, celiac sprue
- 20 (for example arising from gluten induced enteropathy or celiac disease), tropical sprue, hypogammaglobulinemic sprue, mucositis induced by chemotherapy or radiation therapy, diarrhea induced by chemotherapy or radiation therapy, low grade inflammation, metabolic endotoxemia, necrotising enterocolitis, primary biliary cirrhosis, hepatitis, fatty liver disease (including parental nutrition associated gut
- 25 atrophy, PNALD (Parenteral Nutrition-Associated Liver Disease), NAFLD (Non-Alcoholic Fatty Liver Disease) and NASH (Non-Alcoholic Steatohepatitis)), or gastrointestinal side-effects of inflammatory conditions such as pancreatitis or graft versus host disease (GVHD).
- 30 The disclosure also provides a dual agonist of the disclosure for use in a method of reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss.

- 35 The disclosure also provides a dual agonist of the disclosure for use in a method of prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio), diabetes (e.g.

Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome or hypertension.

5 The disclosure also provides a method of increasing intestinal mass, improving intestinal function (especially intestinal barrier function), increasing intestinal blood flow, or repairing intestinal damage or dysfunction in a subject in need thereof, the method comprising administering a dual agonist of the disclosure to the subject.

10 The disclosure also provides a method of prophylaxis or treatment of malabsorption, ulcers (e.g. peptic ulcers, Zollinger-Ellison Syndrome, drug-induced ulcers, and ulcers related to infections or other pathogens), short-bowel syndrome, cul-de-sac syndrome, inflammatory bowel disease (Crohns disease and ulcerative colitis), irritable bowel syndrome (IBS), pouchitis, celiac sprue (for example arising from gluten induced enteropathy or celiac disease), tropical sprue,
15 hypogammaglobulinemic sprue, mucositis induced by chemotherapy or radiation therapy, diarrhea induced by chemotherapy or radiation therapy, low grade inflammation, metabolic endotoxemia, necrotising enterocolitis, primary biliary cirrhosis, hepatitis, fatty liver disease (including parental nutrition associated gut atrophy, PNALD (Parenteral Nutrition-Associated Liver Disease), NAFLD (Non-Alcoholic Fatty Liver Disease) and NASH (Non-Alcoholic Steatohepatitis)), or
20 gastrointestinal side-effects of inflammatory conditions such as pancreatitis or graft versus host disease (GVHD) in a subject in need thereof, the method comprising administering a dual agonist of the disclosure to the subject.

25 The disclosure also provides a method of reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss in a subject in need thereof, the method comprising administering a dual agonist of the disclosure to the subject.

30 The disclosure also provides a method of prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio), diabetes (e.g. Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome or hypertension in a subject in need thereof, the
35 method comprising administering a dual agonist of the disclosure to the subject.

The disclosure also provides the use of a dual agonist of the disclosure in the preparation of a medicament for increasing intestinal mass, improving intestinal function (especially intestinal barrier function), increasing intestinal blood flow, or repairing intestinal damage or dysfunction, e.g. damage to the intestinal epithelium.

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The disclosure also provides the use of a dual agonist of the disclosure in the preparation of a medicament for prophylaxis or treatment of malabsorption, ulcers (e.g. peptic ulcers, Zollinger-Ellison Syndrome, drug-induced ulcers, and ulcers related to infections or other pathogens), short-bowel syndrome, cul-de-sac syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome (IBS), pouchitis, celiac sprue (for example arising from gluten induced enteropathy or celiac disease), tropical sprue, hypogammaglobulinemic sprue, mucositis induced by chemotherapy or radiation therapy, diarrhea induced by chemotherapy or radiation therapy, low grade inflammation, metabolic endotoxemia, necrotising enterocolitis, primary biliary cirrhosis, hepatitis, fatty liver disease (including parental nutrition associated gut atrophy, PNALD (Parenteral Nutrition-Associated Liver Disease), NAFLD (Non-Alcoholic Fatty Liver Disease) and NASH (Non-Alcoholic Steatohepatitis)), or gastrointestinal side-effects of inflammatory conditions such as pancreatitis or graft versus host disease (GVHD).

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The disclosure also provides the use of a dual agonist of the disclosure in the preparation of a medicament for reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss.

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The disclosure also provides the use of a dual agonist of the disclosure in the preparation of a medicament for prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio), diabetes (e.g. Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome or hypertension.

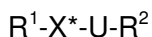
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A further example provides a therapeutic kit comprising a dual agonist, or a pharmaceutically acceptable salt or solvate thereof, according to the disclosure.

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CLAIMS

1. A GLP-1/GLP-2 dual agonist represented by the formula:



wherein:

R¹ is hydrogen (Hy), C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl, preferably R¹ is Hy;

R² is NH₂ or OH, preferably R² is OH;

X* is a peptide of formula I:

H-X2-EG-X5-F-X7-X8-E-X10-X11-TIL-X15-X16-X17-A-X19-X20-X21-FI-X24-WL-X27-X28-X29-KIT-X33 (I)

wherein:

X2 is Aib or G;

X5 is T or S;

X7 is T or S;

X8 is S, E or D;

X10 is L, M, V or Ψ;

X11 is A, N or S;

X15 is D or E;

X16 is G, E, A or Ψ;

X17 is Q, E, K, L or Ψ;

X19 is A, V or S;

X20 is R, K or Ψ;

X21 is D, L or E;

X24 is A, N or S;

X27 is I, Q, K, H or Y;

X28 is Q, E, A, H, Y, L, K, R or S;

X29 is H, Y, K or Q;

X33 is D or E;

U is absent or a sequence of 1-15 residues each independently selected from K, k, E, A, T, I, L and Ψ;

the molecule contains one and only one Ψ , wherein Ψ is a residue of K, k, R, Orn, Dap or Dab in which the side chain is conjugated to a substituent having the formula Z^1 - or Z^1 - Z^2 -, wherein:

Z^1 - is $\text{CH}_3\text{-(CH}_2\text{)}_{10-22}\text{-(CO)-}$ or $\text{HOOC-(CH}_2\text{)}_{10-22}\text{-(CO)-}$; and

$-Z^2$ - is selected from $-Z^{S1}$ -, $-Z^{S1}-Z^{S2}$ -, $-Z^{S2}-Z^{S1}$ -, $-Z^{S2}$ -, $-Z^{S3}$ -, $-Z^{S1}Z^{S3}$ -, $-Z^{S2}Z^{S3}$ -, $-Z^{S3}Z^{S1}$ -, $-Z^{S3}Z^{S2}$ -, $-Z^{S1}Z^{S2}Z^{S3}$ -, $-Z^{S1}Z^{S3}Z^{S2}$ -, $-Z^{S2}Z^{S1}Z^{S3}$ -, $-Z^{S2}Z^{S3}Z^{S1}$ -, $-Z^{S3}Z^{S1}Z^{S2}$ -, $-Z^{S3}Z^{S2}Z^{S1}$ -, $-Z^{S2}Z^{S3}Z^{S2}$ -, wherein:

Z^{S1} is isoGlu, β -Ala, isoLys, or 4-aminobutanoyl;

Z^{S2} is $-(\text{Peg3})_m$ - where m is 1, 2, or 3; and

$-Z^{S3}$ - is a peptide sequence of 1-6 amino acid units independently selected from the group consisting of A, L, S, T, Y, Q, D, E, K, k, R, H, F and G;

and wherein at least one of X5 and X7 is T;

or a pharmaceutically acceptable salt or solvate thereof.

2. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 1 wherein X^* is a peptide of formula II:

H-X2-EG-X5-F-X7-SELATILD-X16-X17-AAR-X21-FIAWLI-X28-X29-KITD (II)

wherein:

X2 is Aib or G;

X5 is T or S;

X7 is T or S;

X16 is G or Ψ ;

X17 is Q, E, K, L or Ψ ;

X21 is D or L;

X28 is Q, E, A, H, Y, L, K, R or S; and

X29 is H, Y or Q.

3. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 1 or claim 2 wherein:

X16 is Ψ and X17 is Q, E, K or L; or

X16 is G and X17 is Ψ .

4. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 1 wherein X* is a peptide of formula V:

H[Aib]EG-X5-F-X7-SELATILD-Ψ-QAARDFIAWLI-X28-X29-KITD (V)

wherein:

X5 is T or S;

X7 is T or S, preferably wherein X5 is S and X7 is T, or X5 is T and X7 is T;

X28 is Q, E, A, H, Y, L, K, R or S;

X29 is H, Y or Q, preferably wherein X29 is H; and

at least one of X5 and X7 is T.

5. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to any one of the preceding claims wherein Ψ is a Lys residue whose side chain is conjugated to the substituent Z¹- or Z¹-Z²-, wherein Z¹- or Z¹-Z²- optionally is selected from:

[17-carboxy-heptadecanoyl]-isoGlu;

[17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3-;

[17-carboxy-heptadecanoyl]-isoGlu-Peg3-;

[19-Carboxy-nonadecanoyl]-isoGlu-;

[19-Carboxy-nonadecanoyl]-isoGlu-KEK-;

[19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3-;

[19-carboxy-nonadecanoyl]-isoGlu-KEK-Peg3-Peg3-;

[19-carboxy-nonadecanoyl]-isoGlu-Peg3-Peg3-;

[19-carboxy-nonadecanoyl]-isoLys-Peg3-Peg3-Peg3-;

[Hexadecanoyl]-βAla-;

[Hexadecanoyl]-isoGlu-; or

Octadecanoyl-.

6. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to any one of the preceding claims wherein Z^1 - is dodecanoyl, tetradecanoyl, hexadecanoyl, octadecanoyl or eicosanoyl.

7. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 5 wherein Z^1 - is:

13-carboxytridecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{12}-(\text{CO})-$;

15-carboxypentadecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{14}-(\text{CO})-$;

17-carboxyheptadecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{16}-(\text{CO})-$;

19-carboxynonadecanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{18}-(\text{CO})-$; or

21-carboxyheneicosanoyl, i.e. $\text{HOOC}-(\text{CH}_2)_{20}-(\text{CO})-$;

and wherein Z^2 is absent or

wherein Z^2 comprises Z^{S1} alone or in combination with Z^{S2} and/or Z^{S3} and where Z^{S1} is optionally bonded to Z^1 and Z^{S2} is optionally bonded to the side chain of the amino acid component of Ψ ,

wherein said, $-Z^{S1}$ - is isoGlu, β -Ala, isoLys, or 4-aminobutanoyl;

$-Z^{S2}$ -, when present, is $-(\text{Peg3})_m$ - where m is 1, 2, or 3; preferably selected from the group consisting of

isoGlu(Peg3)₀₋₃;

β -Ala(Peg3)₀₋₃;

isoLys(Peg3)₀₋₃;

4-aminobutanoyl(Peg3)₀₋₃; or

isoGlu-KEK-(Peg3)₀₋₃,

and wherein $-Z^{S3}$ - is a peptide sequence of 1-6 amino acid units independently selected from the group consisting of A, L, S, T, Y, Q, D, E, K, k, R, H, F and G, such as the peptide sequence KEK.

8. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to any one of the preceding claims, wherein U is absent or wherein U is 1-10 amino acids in length, 1-7 amino acids in length, 3-7 amino acids in length, 1-6 amino acids in length, or 3-6 amino acids in length, optionally wherein U includes at least one charged amino acid, e.g. two or more charged amino acids; or

optionally wherein U includes at least 1 positively charged amino acid and at least one negatively charged amino acid; or

optionally wherein U is a chain of alternately positively and negatively charged amino acids.

9. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 8, wherein U is KEK, EKEKEK, EkEkEk, AKAAEK, AKEKEK or ATILEK or

wherein U is $K_{1-14}\text{-}\Psi$, $K_{1-9}\text{-}\Psi$, $K_{1-6}\text{-}\Psi$, $k_{1-14}\text{-}\Psi$, $k_{1-9}\text{-}\Psi$, $k_{1-6}\text{-}\Psi$, $KE\Psi$, $EKEKE\Psi$, $EkEkEk\Psi$, $AKAAE\Psi$, $AKEKE\Psi$ or $ATILE\Psi$.

10. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to any one of the preceding claims wherein X^* or $X^*\text{-}U$ has the sequence:

H[Aib]EGTFSSELATILD Ψ EAARDFIAWLIEHKITD;

H[Aib]EGSFTSELATILD Ψ EAARDFIAWLIEHKITD;

H[Aib]EGTFTSELATILD Ψ EAARDFIAWLIEHKITD;

H[Aib]EGTFSSELATILD Ψ KAARDFIAWLIEHKITD;

H[Aib]EGSFTSELATILD Ψ KAARDFIAWLIEHKITD;

H[Aib]EGTFTSELATILD Ψ KAARDFIAWLIEHKITD;

H[Aib]EGTFSSELATILDG Ψ AARDFIAWLIEHKITD;

H[Aib]EGSFTSELATILDG Ψ AARDFIAWLIEHKITD;

H[Aib]EGTFTSELATILDG Ψ AARDFIAWLIEHKITD;

H[Aib]EGTFSSELATILD Ψ LAARDFIAWLIEHKITD;

H[Aib]EGSFTSELATILD Ψ LAARDFIAWLIEHKITD;

H[Aib]EGTFTSELATILD Ψ LAARDFIAWLIEHKITD;

H[Aib]EGTFSSELATILD Ψ LAARDFIAWLIAHKITD;

H[Aib]EGSFTSELATILDΨLAARDFAWLIAHKITD;
 H[Aib]EGTFTSELATILDΨLAARDFAWLIAHKITD;
 H[Aib]EGTFTSELATILDΨEAARLFIAWLIEHKITD;
 H[Aib]EGTFSSELATILDΨQAARDFAWLIQHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIQHKITD;
 H[Aib]EGTFTSELATILDΨQAARDFAWLIQHKITD;
 H[Aib]EGTFSSELATILDΨQAARDFAWLIEHKITD;
 H[Aib]EGTFSSELATILDΨQAARDFAWLIAHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIAHKITD;
 H[Aib]EGTFTSELATILDΨQAARDFAWLIAHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIEHKITD;
 H[Aib]EGTFTSELATILDΨQAARDFAWLIEHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIHHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIYHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLILHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIKHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIRHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLISHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLQQHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLYQHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLKQHKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIQQKITD;
 H[Aib]EGSFTSELATILDΨQAARDFAWLIQYKITD;
 H[Aib]EGTFSSELSTILEΨQASREFIAWLIAYKITE;
 H[Aib]EGTFSSELATILDEQAARDFAWLIAHKITDkkkkkΨ;
 H[Aib]EGTFTSELATILDEQAARDFAWLIAHKITDkkkkkΨ;
 H[Aib]EGSFTSELATILDEQAARDFAWLIEHKITDkkkkkΨ;
 H[Aib]EGSFTSEΨATILDEQAARDFAWLIEHKITD;

H[Aib]EGSFTSELATILEGΨAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILDEQAAΨDFIAWLIEHKITD;
H[Aib]EGTFTSELATILDEQAAΨDFIAWLIEHKITD;
H[Aib]EGTFTSEψATILDEQAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILDAψAARDFIAWLIEHKITD; or
H[Aib]EGSFTSELATILDAKAAψDFIAWLIEHKITD.

11. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 10 wherein X* or X*-U has the sequence:

H[Aib]EGTFSSELATILD[K*]EAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILD[K*]EAARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILD[K*]EAARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K*]KAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILD[K*]KAARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILD[K*]KAARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILDG[K*]AARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILDG[K*]AARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILDG[K*]AARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K*]LAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILD[K*]LAARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILD[K*]LAARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K*]LAARDFIAWLIAHKITD;
H[Aib]EGSFTSELATILD[K*]LAARDFIAWLIAHKITD;
H[Aib]EGTFTSELATILD[K*]LAARDFIAWLIAHKITD;
H[Aib]EGTFTSELATILD[K*]EAARLFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K*]QAARDFIAWLIQHKITD;
H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIQHKITD;
H[Aib]EGTFTSELATILD[K*]QAARDFIAWLIQHKITD;

H[Aib]EGTFSSELATILD[K*]QAARDFIAWLIIEHKITD;
 H[Aib]EGTFSSELATILD[K*]QAARDFIAWLIAHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIAHKITD;
 H[Aib]EGTFTSELATILD[K*]QAARDFIAWLIAHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIIEHKITD;
 H[Aib]EGTFTSELATILD[K*]QAARDFIAWLIIEHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIHHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIYHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLILHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIKHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIRHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLISHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLQQHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLYQHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLKQHKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIQQKITD;
 H[Aib]EGSFTSELATILD[K*]QAARDFIAWLIQYKITD;
 H[Aib]EGTFSSELSTILE[K*]QASREFIAWLIAYKITE;
 H[Aib]EGTFSSELATILDEQAARDFIAWLIAHKITDkkkkk[k*];
 H[Aib]EGTFTSELATILDEQAARDFIAWLIAHKITDkkkkk[k*];
 H[Aib]EGSFTSELATILDEQAARDFIAWLIIEHKITDkkkkk[k*];
 H[Aib]EGSFTSE[K*]ATILDEQAARDFIAWLIIEHKITD;
 H[Aib]EGSFTSELATILEG[K*]AARDFIAWLIIEHKITD;
 H[Aib]EGSFTSELATILDEQAA[K*]DFIAWLIIEHKITD;
 H[Aib]EGTFTSELATILDEQAA[K*]DFIAWLIIEHKITD;
 H[Aib]EGTFTSE[K*]ATILDEQAARDFIAWLIIEHKITD;
 H[Aib]EGSFTSELATILDA[K*]AARDFIAWLIIEHKITD; or
 H[Aib]EGSFTSELATILDAKAA[K*]DFIAWLIIEHKITD;

wherein K* or k* indicates an L or D lysine residue respectively in which the side chain is conjugated to the substituent Z¹- or Z¹Z²-.

12. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 11 wherein X* or X*-U has the sequence:

H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]KAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]KAARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]KAARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILDG[K([17-carboxy-heptadecanoyl]-isoGlu)]AARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILDG[K([17-carboxy-heptadecanoyl]-isoGlu)]AARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILDG[K([17-carboxy-heptadecanoyl]-isoGlu)]AARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIEHKITD;
H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIEHKITD;
H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIAHKITD;
H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIAHKITD;
H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIAHKITD;
H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARLFIWLIEHKITD;
H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIIQHKITD;
H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIIQHKITD;
H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIIQHKITD;
H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIEHKITD;
H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIAHKITD;
H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIAHKITD;
H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIAHKITD;

H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIEHKITD;
 H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIEHKITD;
 H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIHHKITD;
 H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIYHKITD;
 H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLILHKITD;
 H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIKHKITD;
 H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIRHKITD;
 H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLISHKITD;
 H[Aib]EGSFTSELATILD[K([Hexadecanoyl]-βAla)]QAARDFIAWLQQHKITD;
 H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]iso-Glu-Peg3)]QAARDFIAWLQYHKITD;
 H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]QAARDFIAWLKQHKITD;
 H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Lys-Peg3-Peg3-Peg3)]QAARDFIAWLIQQKITD;
 H[Aib]EGSFTSELATILD[K(Octadecanoyl)]QAARDFIAWLIQYKITD;
 H[Aib]EGTFSSELSTILE[K(Hexadecanoyl-isoGlu)]QASREFIAWLIAYKITE;
 H[Aib]EGTFSSELATILDEQAARDFIAWLIAHKITDkkkkkk([17-carboxy-Heptadecanoyl]-isoGlu)];
 H[Aib]EGTFTSELATILDEQAARDFIAWLIAHKITDkkkkkk([17-carboxy-Heptadecanoyl]-isoGlu)];
 H[Aib]EGSFTSELATILDEQAARDFIAWLIEHKITDkkkkkk([17-carboxy-Heptadecanoyl]-isoGlu)];
 H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD;
 H[Aib]EGSFTSE[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]ATILDEQAARDFIAWLIEHKITD;
 H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]KAARDFIAWLIEHKITD;
 H[Aib]EGSFTSELATILEG[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]AARDFIAWLIEHKITD;
 H[Aib]EGSFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]DFIAWLIEHKITD;

H[Aib]EGTFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]DFIAWLIHKITD;

H[Aib]EGTFSSELATILD[K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD;

H[Aib]EGTFSSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD;

H[Aib]EGTFSSELATILD[K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIHKITD;

H[Aib]EGTFSSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIHKITD;

H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK)]QAARDFIAWLIQHKITD;

H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD;

H[Aib]EGSFTSE[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]ATILDEQAARDFIAWLIHKITD;

H[Aib]EGTFTSE[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]ATILDEQAARDFIAWLIHKITD;

H[Aib]EGSFTSE[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3)]ATILDEQAARDFIAWLIHKITD;

H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIHKITD;

H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIHKITD;

H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIHKITD;

H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]KAARDFIAWLIHKITD;

H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]QAARDFIAWLIHKITD;

H[Aib]EGSFTSELATILEG[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]AARDFIAWLIHKITD;

H[Aib]EGSFTSELATILDA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]AARDFIAWLIHKITD;

H[Aib]EGSFTSELATILDA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-

Peg3)]AARDFIAWLIEHKITD;

H[Aib]EGSFTSELATILDEQAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIEHKITD;

H[Aib]EGTFTSELATILDEQAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIEHKITD;

H[Aib]EGSFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]DFIAWLIEHKITD;

H[Aib]EGTFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]DFIAWLIEHKITD; or

H[Aib]EGSFTSELATILDAKAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIEHKITD.

13. A dual agonist or pharmaceutically acceptable salt or solvate thereof according to claim 12 which is:

Hy-H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARDFIAWLIEHKITD-OH (Compound 1);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARDFIAWLIEHKITD-OH (Compound 2);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARDFIAWLIEHKITD-OH (Compound 3);

Hy-H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]KAARDFIAWLIEHKITD-OH (Compound 4);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]KAARDFIAWLIEHKITD-OH (Compound 5);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]KAARDFIAWLIEHKITD-OH (Compound 6);

Hy-H[Aib]EGTFSSELATILDG[K([17-carboxy-heptadecanoyl]-isoGlu)]AARDFIAWLIEHKITD-OH (Compound 7);

Hy-H[Aib]EGSFTSELATILDG[K([17-carboxy-heptadecanoyl]-isoGlu)]AARDFIAWLIEHKITD-OH (Compound 8);

Hy-H[Aib]EGTFTSELATILDG[K([17-carboxy-heptadecanoyl]-isoGlu)]AARDFIAWLIEHKITD-OH (Compound 9);

Hy-H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-

isoGlu)]LAARDFIAWLIEHKITD-OH (Compound 10);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIEHKITD-OH (Compound 11);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIEHKITD-OH (Compound 12);

Hy-H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIAHKITD-OH (Compound 13);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIAHKITD-OH (Compound 14);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]LAARDFIAWLIAHKITD-OH (Compound 15);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]EAARLFIAWLIEHKITD-OH (Compound 16);

Hy-H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 17);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 18);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 19);

Hy-H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIEHKITD-OH (Compound 20);

Hy-H[Aib]EGTFSSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIAHKITD-OH (Compound 21);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIAHKITD-OH (Compound 22);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIAHKITD-OH (Compound 23);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIEHKITD-OH (Compound 24);

Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIEHKITD-OH (Compound 25);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIHHKITD-OH (Compound 26);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIYHKITD-OH (Compound 27);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLILHKITD-OH (Compound 28);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIIHKITD-OH (Compound 29);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIRHKITD-OH (Compound 30);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLISHKITD-OH (Compound 31).

Hy-H[Aib]EGSFTSELATILD[K([Hexadecanoyl]-βAla)]QAARDFIAWLQQHKITD-OH (Compound 32);

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]iso-Glu-Peg3)]QAARDFIAWLYQHKITD-OH (Compound 33);

Hy-H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]QAARDFIAWLKQHKITD-OH (Compound 34);

Hy-H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Lys-Peg3-Peg3-Peg3)]QAARDFIAWLIQQKITD-OH (Compound 35);

Hy-H[Aib]EGSFTSELATILD[K(Octadecanoyl)]QAARDFIAWLIQYKITD-OH (Compound 36);

Hy-H[Aib]EGTFSSELSTILE[K(Hexadecanoyl-isoGlu)]QASREFIAWLIAYKITE-OH (Compound 37);

Hy-H[Aib]EGTFSSELATILDEQAARDFIAWLIAHKITDkkkkkk([17-carboxy-Heptadecanoyl]-isoGlu)]-[NH₂] (Compound 38);

Hy-H[Aib]EGTFTSELATILDEQAARDFIAWLIAHKITDkkkkkk([17-carboxy-Heptadecanoyl]-isoGlu)]-[NH₂] (Compound 39);

Hy-H[Aib]EGSFTSELATILDEQAARDFIAWLIEHKITDkkkkkk([17-carboxy-Heptadecanoyl]-isoGlu)]-[NH₂] (Compound 40);

Hy-H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 41);

Hy-H[Aib]EGSFTSE[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]ATILDEQAARDFIAWLIEHKITD-OH (Compound 42);

Hy-H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]KAARDFIAWLIEHKITD-OH (Compound 43);

Hy-H[Aib]EGSFTSELATILEG[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]AARDFIAWLIEHKITD-OH (Compound 44);

Hy-H[Aib]EGSFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-

Peg3)]DFIAWLIEHKITD-OH (Compound 45);

Hy-H[Aib]EGTFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-Peg3-Peg3)]DFIAWLIEHKITD-OH (Compound 46).

Hy-H[Aib]EGTFSSELATILD[K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 47);

Hy-H[Aib]EGTFSSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 48);

Hy-H[Aib]EGTFSSELATILD[K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIEHKITD-OH (Compound 49);

Hy-H[Aib]EGTFSSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIEHKITD-OH (Compound 50);

Hy-H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK)]QAARDFIAWLIQHKITD-OH (Compound 51);

Hy-H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIQHKITD-OH (Compound 52);

Hy-H[Aib]EGSFTSE[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]ATILDEQAARDFIAWLIEHKITD-OH (Compound 53);

Hy-H[Aib]EGTFTSE[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]ATILDEQAARDFIAWLIEHKITD-OH (Compound 54);

Hy-H[Aib]EGSFTSE[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]ATILDEQAARDFIAWLIEHKITD-OH (Compound 55);

Hy-H[Aib]EGTFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIEHKITD-OH (Compound 56);

Hy-H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIEHKITD-OH (Compound 57);

Hy-H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]QAARDFIAWLIAHKITD-OH (Compound 58);

Hy-H[Aib]EGSFTSELATILD[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]KAARDFIAWLIEHKITD-OH (Compound 59);

Hy-H[Aib]EGSFTSELATILD[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]QAARDFIAWLIEHKITD-OH (Compound 60);

Hy-H[Aib]EGSFTSELATILEG[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]AARDFIAWLIEHKITD-OH (Compound 61);

Hy-H[Aib]EGSFTSELATILDA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]AARDFIAWLIEHKITD-OH (Compound 62);

Hy-H[Aib]EGSFTSELATILDA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]AARDFIWLIEHKITD-OH (Compound 63);

Hy-H[Aib]EGSFTSELATILDEQAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIEHKITD-OH (Compound 64);

Hy-H[Aib]EGTFTSELATILDEQAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIEHKITD-OH (Compound 65);

Hy-H[Aib]EGSFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]DFIAWLIEHKITD-OH (Compound 66);

Hy-H[Aib]EGTFTSELATILDEQAA[K([19-carboxy-nonadecanoyl]iso-Glu-KEK-Peg3-Peg3)]DFIAWLIEHKITD-OH (Compound 67); or

Hy-H[Aib]EGSFTSELATILDAKAA[K([19-Carboxy-nonadecanoyl]-isoGlu-KEK-Peg3)]DFIAWLIEHKITD-OH (Compound 68).

14. A composition comprising a dual agonist according to any one of claims 1 to 13, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier,

optionally wherein the carrier is a pharmaceutically acceptable carrier.

15. A dual agonist according to any one of claims 1 to 13, or a composition according to claim 14, for use in therapy.

16. The dual agonist or composition according to claim 15 for use in:

(i) increasing intestinal mass, improving intestinal function, increasing intestinal blood flow, or repairing intestinal damage or dysfunction in a subject in need thereof; or

(ii) the treatment of malabsorption, ulcers, short-bowel syndrome, cul-de-sac syndrome, inflammatory bowel disease, irritable bowel syndrome, pouchitis, celiac sprue, tropical sprue, hypogammaglobulinemic sprue, mucositis induced by chemotherapy or radiation therapy, diarrhea induced by chemotherapy or radiation therapy, low grade inflammation, metabolic endotoxemia, necrotising enterocolitis, primary biliary cirrhosis, hepatitis, fatty liver disease, or gastrointestinal side-effects of inflammatory conditions, in a subject in need thereof; or

(iii) reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss in a subject in need thereof; or

(iv) the treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia, diabetes, pre-diabetes, metabolic syndrome or hypertension in a subject in need thereof.