WO 2018/104561 discloses peptides having dual GLP-1 and GLP-2 agonist activity and proposes medical uses thereof. However, specific dosage regimes for the treatment of obesity and related conditions are not disclosed.

It has now surprisingly been found that the administration of certain peptides having dual GLP-1 and GLP-2 agonist activity at certain dosages results in decreased appetite being observed in patients, without giving rise to the expected side effects of nausea and vomiting. As described herein, effects on appetite reduction with the dual GLP-1 and GLP-2 agonist may occur before (i.e. at lower doses than) nausea and vomiting. This is advantageous over known GLP-1 agonist treatments where the gastrointestinal adverse events (nausea and vomiting) occur before (i.e. at lower doses than) the decreased satiety. This suggests that the dual GLP-1 and GLP-2 agonist may have a better safety profile with regards to gastrointestinal adverse events in indications where appetite reduction is desired. Thus the dosage regime of the invention represents a significant advance on known GLP-1 agonist treatments for obesity.

Summary

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, for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea. Such compounds are referred to in this specification as "GLP-1/GLP-2 dual agonists", or simply "dual agonists". Thus, the compounds according to the present disclosure have activities of both GLP-1 (7-36) and GLP-2 (1-33).

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

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) (SEQ ID NO 1)

wherein:

X2 is Aib or G

The various amino acid positions in peptide X* of the formulae provided here are numbered according to their linear position from N- to C-terminus in the amino acid chain.

In the present context, β-Ala and 3-Aminopropanoyl are used interchangeably.

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;

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;

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;
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.

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.

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.
In some examples, the residues at X27-X29 have a sequence selected from:
IQH;
IEH
IAH;
IHH;
IYH;
ILH;
IKH;
IRH;
ISH;
QQH;
YQH;
KQH;
IQQ;
IQY;
IQT; and
IAY.

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

H-X2-EG-X5-F-X7-SELATILD-X16-X17-AAR-X21-FIAWLI-X28-X29-KITD (II) (SEQ ID NO 2)

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;

X29 is H, Y or Q;

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.

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.

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) (SEQ ID NO 3)

wherein:

X5 is T or S;

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;

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.

X* may be a peptide of formula IV:
H[Aib]EG-X5-F-X7-SELATILD-X16-X17-AAR-X21-FIAWLI-X28-X29-KITD (IV) (SEQ ID NO 4)
wherein:
X5 is T or S;
X7 is T or S;
X16 is G or Ψ;
X17 is E, K, L or Ψ;
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.

In some examples of any of formulae I to IV, X16 is Ψ and X17 is E, K or L.

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

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

X* may be a peptide of formula V:
H[Aib]EG-X5-F-X7-SELATILD-Ψ-QAARDFIAWLI-X28-X29-KITD (V) (SEQ ID NO 5)
wherein
X5 is T or S;
X7 is T or S;
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 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;
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.

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-.

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:
13-carboxytridecanoyl, i.e. HOOC–$(CH_2)_{12}$–(CO)–;
15-carboxypentadecanoyl, i.e. HOOC–$(CH_2)_{14}$–(CO)–;
17-carboxyheptadecanoyl, i.e. HOOC–$(CH_2)_{16}$–(CO)–;
19-carboxynonadecanoyl, i.e. HOOC–$(CH_2)_{18}$–(CO)–; or
21-carboxyheneicosanoyl, i.e. HOOC–$(CH_2)_{20}$–(CO)–.

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}.
In such examples:
-Z^{S1}- is isoGlu, β-Ala, isoLys, or 4-aminobutanoyl;
-Z^{S2}-, when present, is -$(Peg3)_m$- 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, such as the peptide 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.

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, -Z^2- is:
isoGlu-KEK-(Peg3)$_{0-3}$ (SEQ ID NO 6).

Specific examples of the substituent Z^1-Z^2- are set out below. In some examples, Z^1-Z^2- is [17-carboxy-heptadecanoyl]-isoGlu. For example, Ψ may be K([17-carboxy-heptadecanoyl]-isoGlu). In some examples, Z^1-Z^2 - is:
[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-.

For example, Ψ may be:
K([17-Carboxy-heptadecanoyl]-isoGlu-KEK-Peg3);
K([17-carboxy-heptadecanoyl]-isoGlu-Peg3);
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);
K([19-carboxy-nonadecanoyl]-isoLys-Peg3-Peg3-Peg3);
K([Hexadecanoyl]-βAla-;
K([Hexadecanoyl]-isoGlu); or

K(Octadecanoyl).

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.

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.

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.

Further examples of peptide sequences U include KEK, EKEKEK (SEQ ID NO 7), EkEkEk (SEQ ID NO 8), AKAAEK (SEQ ID NO 9), AKEKEK (SEQ ID NO 10) and ATILEK (SEQ ID NO 11).

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}-Ψ, K_{1-9}-Ψ and K_{1-6}-Ψ, e.g., K_2-Ψ, K_3-Ψ, K_4-Ψ, K_5-Ψ and K_6-Ψ, especially K_4-Ψ and K_5.-Ψ. Yet further examples include k_{1-14}-Ψ, k_{1-9}-Ψ, and k_{1-6}-Ψ, e.g. k_2-Ψ, k_3-Ψ, k_4-Ψ, k_5-Ψ and k_6-Ψ especially k_4-Ψ and k_5-Ψ. Yet further examples include KEΨ, EKEKEΨ (SEQ ID NO 12), EkEkEΨ (SEQ ID NO 13) AKAAEΨ (SEQ ID NO 14), AKEKEΨ (SEQ ID NO 15) and ATILEΨ (SEQ ID NO 16).

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*-U may have the sequence:

H[Aib]EGTFSSELATILDΨEAARDFIAWLIEHKITD (SEQ ID NO 17);

H[Aib]EGSFTSELATILDΨEAARDFIAWLIEHKITD (SEQ ID NO 18);

H[Aib]EGTFTSELATILDΨEAARDFIAWLIEHKITD (SEQ ID NO 19);

H[Aib]EGTFSSELATILDΨKAARDFIAWLIEHKITD (SEQ ID NO 20);

H[Aib]EGSFTSELATILDΨKAARDFIAWLIEHKITD (SEQ ID NO 21);

H[Aib]EGTFTSELATILDΨKAARDFIAWLIEHKITD (SEQ ID NO 22);

H[Aib]EGTFSSELATILDGΨAARDFIAWLIEHKITD (SEQ ID NO 23);

H[Aib]EGSFTSELATILDGΨAARDFIAWLIEHKITD (SEQ ID NO 24);

H[Aib]EGTFTSELATILDGΨAARDFIAWLIEHKITD (SEQ ID NO 25);

H[Aib]EGTFSSELATILDΨLAARDFIAWLIEHKITD (SEQ ID NO 26);

H[Aib]EGSFTSELATILDΨLAARDFIAWLIEHKITD (SEQ ID NO 27);

H[Aib]EGTFTSELATILDΨLAARDFIAWLIEHKITD (SEQ ID NO 28);

H[Aib]EGTFSSELATILDΨLAARDFIAWLIAHKITD (SEQ ID NO 29);

H[Aib]EGSFTSELATILDΨLAARDFIAWLIAHKITD (SEQ ID NO 30);

H[Aib]EGTFTSELATILDΨLAARDFIAWLIAHKITD (SEQ ID NO 31);

H[Aib]EGTFTSELATILDΨEAARLFIAWLIEHKITD (SEQ ID NO 32);

H[Aib]EGTFSSELATILDΨQAARDFIAWLIQHKITD (SEQ ID NO 33);

H[Aib]EGSFTSELATILDΨQAARDFIAWLIQHKITD (SEQ ID NO 34);

H[Aib]EGTFTSELATILDΨQAARDFIAWLIQHKITD (SEQ ID NO 35);

H[Aib]EGTFSSELATILDΨQAARDFIAWLIEHKITD (SEQ ID NO 36);

H[Aib]EGTFSSELATILDΨQAARDFIAWLIAHKITD (SEQ ID NO 37);

H[Aib]EGSFTSELATILDΨQAARDFIAWLIAHKITD (SEQ ID NO 38);

H[Aib]EGTFTSELATILDΨQAARDFIAWLIAHKITD (SEQ ID NO 39);

H[Aib]EGSFTSELATILDΨQAARDFIAWLIEHKITD (SEQ ID NO 40);

H[Aib]EGTFTSELATILDΨQAARDFIAWLIEHKITD (SEQ ID NO 41);

H[Aib]EGSFTSELATILDΨQAARDFIAWLIHHKITD (SEQ ID NO 42);

H[Aib]EGSFTSELATILDΨQAARDFIAWLIYHKITD (SEQ ID NO 43);

H[Aib]EGSFTSELATILDΨQAARDFIAWLILHKITD (SEQ ID NO 44);

H[Aib]EGSFTSELATILDΨQAARDFIAWLIKHKITD (SEQ ID NO 45);

H[Aib]EGSFTSELATILDΨQAARDFIAWLIRHKITD (SEQ ID NO 46);

H[Aib]EGSFTSELATILDΨQAARDFIAWLISHKITD (SEQ ID NO 47);

H[Aib]EGSFTSELATILDΨQAARDFIAWLQQHKITD (SEQ ID NO 48);

H[Aib]EGSFTSELATILDΨQAARDFIAWLYQHKITD (SEQ ID NO 49);

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)]AARDFIAWLIEHKITD-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).

In one example the dual agonist is H[Aib]EGSFTSELATILD[Ψ]QAARDFIAWLIQHKITD (SEQ ID NO 34). In one example the dual agonist is:

a. Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (CPD1OH); or
b. Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-NH2 (CPD1NH2).

In a preferred example the dual agonist is Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 18).

In a preferred example the dual agonist is Hy-H[Aib]EGTFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 19).

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

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 for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid

obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, wherein the method comprises administering the dual agonist to the patient at a dose of about 0.1 mg to about 10.0 mg. 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.
The disclosure also provides a dual agonist according to 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 wherein the method comprises administering the dual agonist to the patient at a dose of about 0.1 mg to about 10.0 mg.

The disclosure also provides a dual agonist according to the disclosure for use in a method of prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea wherein the method comprises administering the dual agonist to the patient at a dose of about 0.1 mg to about 10.0 mg.

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 according to the disclosure to the subject at a dose of about 0.1 mg to about 10.0 mg.

The disclosure also provides a method of prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, the method comprising administering a dual agonist according to the disclosure to the subject at a dose of about 0.1 mg to about 10.0 mg.

The disclosure also provides the use of a dual agonist according to 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 wherein the medicament is administered to the patient at a dose of about 0.1 mg to about 10.0 mg.

The disclosure also provides the use of a dual agonist according to the disclosure in the preparation of a medicament for prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea wherein the medicament is administered to the patient at a dose of about 0.1 mg to about 10.0 mg.

A further example provides a therapeutic kit comprising a dual agonist, or a pharmaceutically acceptable salt or solvate thereof, according to the disclosure for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, or for reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss, wherein the method comprises administering the dual agonist to the patient at a dose of about 0.1 mg to about 10.0 mg.

In one example the patient or subject (terms used interchangeably herein) may experience enhanced satiety following administration of the dual agonist.

In one aspect, the present disclosure refers to the use of a GLP-1/GLP-2 dual agonist which is Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 18) or a pharmaceutically acceptable salt or solvate thereof; in the manufacture of a medicament for reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea; wherein the dual agonist is to be administered to the patient at a dose of 1.5 mg to 10.0 mg.

Figures

Figure 1: Mean pharmacokinetic profiles of Cpd. 18 following single dose to healthy subjects.

Figure 2: Multi-ascending dose study design. Upper lines denote number of patients treated with Cpd. 18, lower lines denote placebo administration, diamonds represent safety evaluation.

Figure 3: Change in body weight following multi-ascending dose in phase 1b study.

Figure 4: Illustration of the randomised (2:2:1:1) parallel-group, double-blind, placebo-controlled study design in which 54 individuals with obesity will receive either 1) compound 18 2/4/6 mg, 2) compound 18 2/4 mg, 3) placebo 2/4/6 mg, or 4) placebo 2/4 mg for a period of 12 weeks

Detailed Description of the Invention

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in

Claims

1. Use of a GLP-1/GLP-2 dual agonist which is Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (Compound 18)
or a pharmaceutically acceptable salt or solvate thereof;
in the manufacture of a medicament for reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea;
wherein the dual agonist is to be administered to the patient at a dose of 1.5 mg to 10.0 mg.

2. The use according to claim 1 wherein the dual agonist is to be administered to the patient at a dose of 1.5 mg to 8.0 mg.

3. The use according to any one of the preceding claims wherein the dual agonist is to be administered to the patient at a dose of 1.5 to 7.5 mg, preferably 1.5 to 6.0 mg, preferably 1.5 to 4.0 mg, preferably 1.5 to 3.5 mg.

4. The use according to any one of the preceding claims wherein the dual agonist is to be administered to the patient at a dose of 2.0 to 7.5 mg, preferably 2.0 to 6.0 mg, preferably 2.0 to 4.0 mg, preferably 2.0 to 3.5 mg, preferably 2.25 to 3.5 mg.

5. The use according to any one of the preceding claims wherein the dual agonist is to be administered to the patient at a dose of 1.5 mg, 2.0 mg, 2.25 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 9.0 mg or 10.0 mg.

6. The use according to any one of the preceding claims wherein the patient is to be administered 1, 2, 3 or 4 lower doses of the dual agonist or pharmaceutically acceptable salt or solvate thereof, followed by at least one higher dose of the dual agonist or pharmaceutically acceptable salt or solvate thereof.

7. The use according to claim 6, wherein said lower dose is between 1.5 mg and 3.5mg.

8. The use according to claim 6 or claim 7, wherein said higher dose is between 6.0 mg and 8.5 mg.

9. The use according to any one of the preceding claims wherein the dual agonist is to be administered to the patient by injection, preferably by subcutaneous injection.

10. The use according to any one of the preceding claims wherein the patient is a human.

11. The use according to any one of the preceding claims wherein the patient does not experience side-effects of nausea and/or vomiting following administration of the dual agonist.

12. The use according to any one of the preceding claims, wherein the dual agonist is to be administered once-weekly.

13. The use according to any one of the preceding claims wherein said dual agonist or pharmaceutically acceptable salt or solvate thereof is in the form of a composition comprising the dual agonist in admixture with a carrier, wherein preferably the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier.

14. The use according to claim 13 wherein the pharmaceutical composition is an isotonic parenteral composition.

15. The use according to claim 14 wherein the pharmaceutical composition is an isotonic parenteral composition comprising:
a) 5 mM to 50 mM of phosphate buffer component, preferably 10 mM to 40 mM, more preferably 15 mM to 30 mM, and most preferably 20 mM of phosphate buffer component; and
b) 190 mM to 240 mM of one or more tonicity agent, wherein said one or more tonicity agent comprises or is, preferably is, a non-ionic tonicity agent, and wherein the non-ionic tonicity agent is mannitol,
wherein said composition further comprises a solvent, and
wherein said composition has a pH of pH 6.0 to pH 8.2, preferably a pH of pH 7.0 to pH 8.0.