

COMBINATION THERAPY

FIELD OF THE INVENTION

- 5 The present invention relates to the use of a combination of an amylin analogue and a dual agonist of the gastric inhibitory polypeptide receptor (GIPR) and the glucagon-like peptide-1 receptor (GLP-1R) to regulate body weight and to treat or prevent obesity and related conditions.

10 BACKGROUND TO THE INVENTION

- Obesity is a currently a significant public health issue across much of the developed world and is correlated with the development of several serious conditions, such as cardiovascular disease, type 2 diabetes, sleep apnoea, and certain cancers. The standard treatment for
- 15 obesity is lifestyle intervention, including the reduction of energy intake and the increase of exercise. However, while such interventions can achieve temporary success, it is often challenging for patients to sustain such lifestyle changes over a long period such that the weight loss achieved is permanent.

20 Amylin

- Amylin is one of a family of peptide hormones that includes amylin, calcitonin, calcitonin gene-related peptide, adrenomedullin and intermedin (intermedin also being known as AFP-6), and has been implicated in various metabolic diseases and disorders. Human amylin was first isolated, purified and characterized as the major component of amyloid deposits in the
- 25 islets of pancreases from type 2 diabetes patients.

Native human amylin is a 37-amino acid peptide having the sequence:

Hy-KC()₁NTATC()₂ATQRLANFLVHSSNNFGAILSSTNVGSNTY-NH₂
(SEQ ID NO: 5)

- 30 wherein Hy- at the N-terminus designates a hydrogen atom, corresponding to the presence of a free amino group on the N-terminal amino acid residue [i.e. the lysine (K) residue at sequence position number 1 in the sequence shown above], wherein -NH₂ at the C-terminus indicates that the C-terminal carboxyl group is in the amide form, and wherein the parentheses “()” associated with the two cysteine (C, Cys) residues at sequence positions 2
- 35 and 7 indicate the presence of an intramolecular disulfide bridge between the two Cys residues.

Amylin may be beneficial in treating metabolic disorders such as diabetes and/or obesity. Amylin is believed to slow gastric emptying, suppress glucagon secretion and reduce food intake, thereby regulating the rate of glucose release to the circulation. Amylin appears to complement the actions of insulin. Compared to healthy adults, type 1 diabetes patients
5 have no circulating amylin, and type 2 diabetes patients exhibit reduced postprandial amylin concentrations. WO 93/10146 describes an amylin analogue known as pramlintide, which has the sequence:

Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-
Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr (SEQ ID
10 NO: 6).

Pramlintide also possesses a disulphide bridge between the cysteine residues at positions 2 and 7, and, in human trials, has been shown to reduce body weight or reduce weight gain.

An alternative amylin analogue incorporating N-methylated residues and having a reduced
15 tendency to fibrillation, designated IAPP-GI, has been described by Yan et al. (PNAS, 103(7), 2046-2051, 2006; Angew. Chem. Int. Ed. 2013, 52, 10378-10383; WO2006/042745). IAPP-GI appears to have lower activity than native amylin, however.

WO 2018/046719 describes amylin analogues having, inter alia, a lactam bridge instead of a
20 disulfide bridge, N-methylated residues, and a deletion corresponding to the residues Asn21 and Asn22 of native human amylin. Such analogues have considerably lower tendency towards fibrillation than native amylin, while also having higher potency than the analogues described by Yan et al. (supra).

25 GIP and GLP-1

GIP and GLP-1 are peptide hormones known as incretins which have roles in glucose homeostasis.

Gastric inhibitory polypeptide or gastric inhibitory peptide (GIP), also known as glucose-
30 dependent insulinotropic polypeptide, is a 42-amino acid peptide hormone produced by the mucosa of the small intestine. In the presence of glucose, GIP stimulates insulin secretion from pancreatic β -cells by binding and agonising the GIP receptor (GIPR) on the β -cell surface.

35 Glucagon-like peptide-1 (GLP-1) is a peptide hormone produced by intestinal tissue. When secreted from the gastrointestinal tract in response to nutrient ingestion, GLP-1 potentiates glucose-stimulated insulin secretion from β -cells (Kim and Egan, 2008, Pharmacol.Rev. 470-

512). Furthermore, GLP-1 or its analogues has been shown to increase somatostatin secretion and suppress glucagon secretion (Holst JJ, 2007, *Physiol Rev.* 1409-1439). The sequence of human GLP-1 is:

Hy-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gly-Gln-Ala-Ala-
5 Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly-NH₂ (SEQ ID NO: 7)

GLP-1 binds and agonises the GLP-1 receptor (GLP-1R), which is expressed on pancreatic β -cells and brain neurons.

Besides the primary actions of GLP-1 on glucose-stimulated insulin secretion, GLP-1 is also
10 known as a key regulator of appetite, food intake, and body weight. Moreover, GLP-1 can inhibit gastric emptying and gastrointestinal motility in both rodents and humans, most likely through GLP-1 receptors present in the gastrointestinal tract (Holst JJ, 2007, *Physiol Rev.* 1409-1439; Hellström et al., 2008, *Neurogastroenterol Motil.* Jun; 20(6):649-659). In addition, GLP-1 seems to have insulin-like effects in major extrapancreatic tissues,
15 participating in glucose homeostasis and lipid metabolism in tissues such as muscle, liver, and adipose tissues (Kim and Egan, 2008, *Pharmacol.Rev.* 470-512).

GLP-1 is released from the gut in response to food intake and hence acts as a satiety signal, leading to reduced food intake (Madsbad, S., 2014, *Diabetes Obes Metab.* 16: 9-21). There
20 is evidence to suggest that the effect of GLP-1 may be impaired in obese subjects, suggesting that GLP-1 agonists may have promise in the treatment of obesity.

GLP-1 has been mostly reported to augment an insulin response after an oral intake of glucose or fat. It is, however, generally understood that GLP-1 lowers glucagon
25 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.

Molecules which exhibit both GIP activity and GLP-1 activity (i.e. agonise both GIPR and GLP-1R) are known in the art (see for example WO 2011/119657, WO 2013/164483 and
30 WO 2014/192284) and are referred to herein as GIPR / GLP-1R dual agonists. WO 2016/111971 describes a GIPR / GLP-1R dual agonist called tirzepatide, which has been approved in the US, EU, Canada and Australia for treatment of type 2 diabetes. Tirzepatide is also described in Chavda et al. 2022 (Chavda et al. Tirzepatide, a New Era of Dual-Targeted Treatment for Diabetes and Obesity: A Mini-Review. *Molecules* 2022, 27, 4315).

35

SUMMARY OF THE INVENTION

Broadly, the present invention relates to therapies and methods for treating or preventing diseases and disorders related to excess body weight. More specifically, the invention is
5 based on the surprising finding that the combination of the use of an amylin analogue and a GIPR / GLP-1R dual agonist results in greater treatment efficacy as compared with treatment of either agent alone.

Thus, the invention provides a combination of an amylin analogue and a gastric inhibitory
10 polypeptide receptor (GIPR) / glucagon-like peptide-1 receptor (GLP-1R) dual agonist for use in treating or preventing a disease in a subject, wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes.

In one aspect, the invention provides a combination of an amylin analogue and a gastric
15 inhibitory polypeptide receptor (GIPR) / glucagon-like peptide-1 receptor (GLP-1R) dual agonist for use in treating or preventing a disease in a subject, wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes; wherein the amylin analogue and the gastric inhibitory polypeptide receptor (GIPR) / glucagon-like peptide-1 receptor (GLP-1R) dual agonist are administered by any one of
20 separately, simultaneously, consecutively, concomitantly, together, or in the same formulation to a subject.

The invention also provides a combination of an amylin analogue and a GIPR / GLP-1R dual
agonist for use in a method of inhibiting weight gain and/or reducing body weight in a
25 subject.

In one aspect, the invention provides a combination of an amylin analogue and a GIPR /
GLP-1R dual agonist for use in a method of inhibiting weight gain and/or reducing body
weight in a subject; wherein the amylin analogue and the GIPR / GLP-1R dual agonist are
30 administered by any one of separately, simultaneously, consecutively, concomitantly, together, or in the same formulation to a subject.

The invention also provides a kit comprising an amylin analogue and a GIPR / GLP-1R dual
agonist.

35 Preferably, the amylin analogue is petrelintide

[19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTHyp-NH₂ (SEQ ID NO: 2) as described herein.

Preferably the GIPR / GLP-1R dual agonist is Hy-

- 5 Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]AFVQWLIAGGPSSGAPPPS-NH₂ (SEQ ID NO: 4) (tirzepatide) as described herein.

BRIEF DESCRIPTION OF THE FIGURES

- 10 **Figure 1** depicts diagrammatically the study design used in Example 1.

Figure 2 shows the mean cumulated food intake $\pm$ SEM in g/rat of rats administered vehicle (group 1, black circles), vehicle and then from day 14 vehicle and amylin analogue (group 2, white circles), tirzepatide and then from day 14 tirzepatide and vehicle (group 3, black squares), or tirzepatide and then from day 14 tirzepatide and amylin analogue (group 4, white squares).

Figure 3 shows the mean cumulated water intake $\pm$ SEM in g/rat of rats administered vehicle (group 1, black circles), vehicle and then from day 14 vehicle and amylin analogue (group 2, white circles), tirzepatide and then from day 14 tirzepatide and vehicle (group 3, black squares), or tirzepatide and then from day 14 tirzepatide and amylin analogue (group 4, white squares).

Figure 4 shows the mean % body weight change $\pm$ SEM of rats administered vehicle (group 1, black circles), vehicle and then from day 14 vehicle and amylin analogue (group 2, white circles), tirzepatide and then from day 14 tirzepatide and vehicle (group 3, black squares), or tirzepatide and then from day 14 tirzepatide and amylin analogue (group 4, white squares).

Figure 5 depicts the structure of the GIPR / GLP-1R dual agonist tirzepatide. The majority of amino acids in the peptide portion of tirzepatide are depicted using one-letter code. The exceptions are α -aminoisobutyric acid (Aib) at positions 2 and 13, and lysine at position 20, which are each depicted using chemical structure notation. The linker and fatty acid moiety conjugated to the side-chain of lysine at position 20 ((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)₁-CO-(CH₂)₁₈-COOH) is also depicted using chemical structure notation. The “H-” moiety at the N-terminus indicates the presence of a primary amine group and the “-NH₂” moiety at the C-terminus indicates the presence of an amido (CONH₂) group at the C-terminus (rather than a carboxylic acid group -COOH).

Figure 6 shows the mean exposure of amylin analogue on day 34 in rats administered amylin analogue alone (chequered bars) or amylin analogue and tirzepatide (striped bars) as described in Example 1 herein.

5

Figure 7 shows the mean exposure of tirzepatide on day 34 in rats administered tirzepatide alone (crossed bars) or amylin analogue and tirzepatide (striped bars) as described in Example 1 herein.

10 **Figure 8** shows the individual exposure values of amylin analogue on day 34 in rats administered amylin analogue alone (white circles) or amylin analogue and tirzepatide (white squares) as described in Example 1 herein.

15 **Figure 9** shows the individual exposure values of tirzepatide on day 34 in rats administered tirzepatide alone (black squares) or amylin analogue and tirzepatide (white squares) as described in Example 1 herein.

20 **Figure 10** shows the mean weight change at day 34 of rats administered vehicle, amylin analogue alone, tirzepatide alone or amylin analogue and tirzepatide as described in Example 1 herein.

DETAILED DESCRIPTION OF THE INVENTION

25 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 the art. Generally, nomenclature used in connection with, and techniques of, chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

30

All patents, published patent applications and non-patent publications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

35 Each embodiment of the invention described herein may be taken alone or in combination with one or more other embodiments of the invention.

Definitions

Unless specified otherwise, the following definitions are provided for specific terms which are used in the present written description. All other terms will be understood as having a meaning that is common in the art as would be attributed to them by the person skilled in the art.

Throughout this specification, the word “comprise”, and grammatical variants thereof, such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated integer or component, or group of integers or components, but not the exclusion of any other integer or component, or group of integers or components.

The singular forms “a,” “an,” and “the” include the plurals unless the context clearly dictates otherwise.

The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” may be used interchangeably.

The terms “patient”, “subject” and “individual” are used interchangeably herein and refer to either a human or a non-human animal. These terms include mammals such as humans, primates, livestock animals (e.g. bovines and porcines), companion animals (e.g. canines and felines) and rodents (e.g. mice and rats).

“Percent (%) amino acid sequence identity” with respect to a peptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical to the amino acid residues in the wild-type (human) GLP-2 sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Sequence alignment can be carried out by the skilled person using techniques well known in the art, for example using publicly available software such as BLAST, BLAST2 or Align software. For examples, see Altschul et al., Methods in Enzymology 266: 460-480 (1996) or Pearson et al., Genomics 46: 24-36, 1997.

The percentage sequence identities used herein in the context of the present invention may be determined using these programs with their default settings. More generally, the skilled worker can readily determine appropriate parameters for determining alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

Agonist peptides

The invention relates to therapeutic use of agonist peptides, in particular an amylin analogue and a GIPR /GLP-1R dual agonist. The term “agonist” as employed in the context of the invention refers to a substance (i.e. peptide, molecule or ligand) that activates the receptor type in question. The terms “peptides”, “compounds”, “molecules” and “agonists” may be used herein to refer collectively to both the amylin analogue and the GIPR /GLP-1R dual agonist.

- Throughout the present description and claims, in representing agonist peptides the conventional three-letter and one-letter codes for naturally occurring amino acids are used, i.e.:
- A (Ala), G (Gly), L (Leu), I (Ile), V (Val), F (Phe), W (Trp), S (Ser), T (Thr), Y (Tyr), N (Asn), Q (Gln), D (Asp), E (Glu), K (Lys), R (Arg), H (His), M (Met), C (Cys) and P (Pro);
- as well as generally accepted three-letter codes for other α -amino acids, such as 4-hydroxyproline, also referred to herein as hydroxyproline (e.g. (2S,4R)-4-hydroxyproline [also denoted (4R)-4-hydroxy-L-proline]) (Hyp or 4Hyp), sarcosine (Sar), norleucine (Nle), α -aminoisobutyric acid (Aib), 1-Naphthylalanine (1-Nal), 2,3-diaminopropanoic acid (Dap), 2,4-diaminobutanoic acid (Dab) and 2,5-diaminopentanoic acid (ornithine; Orn). Such other α -amino acids may be shown in square brackets “[]” (e.g. “[Aib]”) when used in a general formula or sequence in the present specification, especially when the rest of the formula or sequence is shown using the single letter code. Unless otherwise specified, amino acid residues in peptides of the invention are of the L-configuration. However, D-configuration amino acids may be incorporated. In the present context, an amino acid code written with a small letter represents the D-configuration of said amino acid, e.g. “k” represents the D-configuration of lysine (K).

- Among sequences disclosed herein are sequences incorporating a “Hy-” or “H-” moiety at the amino terminus (N-terminus) of the sequence, and either an “-OH” moiety or an “-NH₂” moiety at the carboxy terminus (C-terminus) of the sequence. In such cases, and unless otherwise indicated, a “Hy-” or “H-” moiety at the N-terminus of the sequence in question indicates a hydrogen atom [i.e. R¹ = hydrogen = Hy in the general formulas], corresponding to the presence of a free primary or secondary amino group at the N-terminus. An “-OH” moiety at the C-terminus of the sequence indicates a hydroxy group [e.g. R² = OH in general formulas], corresponding to the presence of a carboxy (COOH) group at the C-terminus. An “-NH₂” moiety at the C-terminus of the sequence indicates an amino group [e.g. R² = NH₂ in the general formulas], corresponding to the presence of an amido (CONH₂) group at the C-

terminus. In each sequence of the invention, a C-terminal “-OH” moiety may be substituted for a C-terminal “-NH₂” moiety, and vice-versa.

The agonist peptides (i.e. the amylin analogue or GIPR / GLP-1R dual agonist) may be in the form of a pharmaceutically acceptable salt or solvate, such as a pharmaceutically acceptable acid addition salt. Thus, it is to be understood that any reference herein to an amylin analogue encompasses pharmaceutically acceptable salts and solvates thereof. Likewise, any reference herein to a GIPR / GLP-1R dual agonists encompasses pharmaceutically acceptable salts and solvates thereof.

Suitable salts formed with bases include metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts; ammonia salts and organic amine salts, such as those formed with morpholine, thiomorpholine, piperidine, pyrrolidine, a lower mono-, di- or tri-alkylamine (e.g., ethyl-tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine), or a lower mono-, di- or tri-(hydroxyalkyl)amine (e.g., mono-, di- or triethanolamine). Internal salts may also be formed. Similarly, when a compound of the present invention contains a basic moiety, salts can be formed using organic or inorganic acids. For example, salts can be formed from the following acids: formic, acetic, propionic, butyric, valeric, caproic, oxalic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric, benzoic, carbonic, uric, methanesulphonic, naphthalenesulphonic, benzenesulphonic, toluenesulphonic, p-toluenesulphonic (i.e. 4-methylbenzene-sulphonic), camphorsulphonic, 2-aminoethanesulphonic, aminomethylphosphonic and trifluoromethanesulphonic acid (the latter also being denoted triflic acid), as well as other known pharmaceutically acceptable acids. Amino acid addition salts can also be formed with amino acids, such as lysine, glycine, or phenylalanine.

The term “solvate” in the context of the present invention refers to a complex of defined stoichiometry formed between a solute (*in casu*, a peptide or pharmaceutically acceptable salt thereof according to the invention) and a solvent. The solvent in this connection may, for example, be water, ethanol or another pharmaceutically acceptable, typically small-molecular organic species, such as, but not limited to, acetic acid or lactic acid. When the solvent in question is water, such a solvate is normally referred to as a hydrate.

Sequence identity

In some embodiments, the amylin analogue and/or a GIPR /GLP-1R dual agonist is defined as comprising a variant of an amino acid sequence (which may be referred to herein as a

“reference sequence”), wherein the variant has at least a certain percentage sequence identity to the reference sequence. The terms “percentage (%) sequence identity”, “sequence identity” and “identity” are used interchangeably herein.

- 5 In some embodiments, “percentage (%) sequence identity” of the variant is defined as the percentage of amino acids in the amino sequence of the variant that are identical to the amino acids in the reference sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percentage sequence identity, and not considering any conservative substitutions as part of the sequence identity. Sequence alignment can be
- 10 carried out by the skilled person using techniques well known in the art, for example using publicly available software such as BLAST, BLAST2 or Align software. For examples, see Altschul et al., Methods in Enzymology 266: 460-480 (1996) or Pearson et al., Genomics 46: 24-36, 1997. The percentage sequence identities used herein in the context of the present invention may be determined using these programs with their default settings. More
- 15 generally, the skilled worker can readily determine appropriate parameters for determining alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

- In some embodiments, the variant has at least 80% sequence identity to the reference sequence, such as at least 85% sequence identity, such as at least 90% sequence identity, such as at least 95% sequence identity, such as at least 96% sequence identity, such as at least 97% sequence identity, such as at least 98% sequence identity, such as at least 99% sequence identity, such as 100% identity to the reference sequence.

25 **Amylin analogues**

- An amylin analogue is a molecule that is an amylin receptor agonist, i.e. the molecule is capable of binding to, and inducing signaling by, one or more receptors or receptor complexes regarded as physiological receptors for human amylin. The terms “amylin analogue” and “amylin receptor agonist” are used interchangeably herein. Amylin analogues
- 30 may also be referred to as compounds, molecules or peptides herein.

An amylin analogue according to the invention may be a molecule of the formula:



wherein:

- 35 R^1 is hydrogen, C_{1-4} acyl, benzoyl or C_{1-4} alkyl, or a half-life extending moiety M, wherein M is optionally linked to Z via a linker moiety L;
- R^2 is OH or NHR^3 , wherein R^3 is hydrogen or C_{1-3} -alkyl; and

Z is an amino acid sequence of formula I:

X1-X2-X3-X4-X5-X6-X7-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-X27-Ser-Ser-Thr-Glu-X32-Gly-Ser-X35-Thr-X37 (SEQ ID NO: 1)

5 wherein:

X1 is selected from the group consisting of Arg, Lys and Glu;

X2 and X7 are amino acid residues whose side chains together form a lactam bridge;

X3 is selected from the group consisting of Gly, Gln and Pro;

X4 is selected from the group consisting of Thr and Glu;

10 X5 is selected from the group consisting of Ala and Leu;

X6 is selected from the group consisting of Thr and Ser;

X10 is selected from the group consisting of Glu and Gln;

X14 is selected from the group consisting of Aad, His, Asp, Asn and Arg;

X17 is selected from the group consisting of Gln, His and Thr;

15 X19-X20 is selected from Ser-Ser, Thr-Thr, Ala-Thr, Ala-Ala, Gly-Thr, Gly-Gly and Ala-Asn or is absent;

X27 is selected from the group consisting of Leu and Pro;

X32 is selected from the group consisting of Val and Thr;

X35 is selected from the group consisting of Asn and Ser;

20 X37 is selected from the group consisting of Hyp and Pro; and

Hyp is 4-hydroxyproline, e.g. (2S,4R)-4-hydroxyproline [also denoted (4R)-4-hydroxy-L-proline],

Gly(Me) is N-methylglycine [also known as sarcosine (Sar)],

Ile(Me) is N-methylisoleucine, and

25 Aad is 2-aminoadipic acid, e.g. (2S)-2-aminoadipic acid [also (2S)-2-aminohexanedioic acid], also known as homo-glutamic acid;

or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the amylin analogue comprises the amino acid sequence

30 RDGTATKATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-Hyp (SEQ ID NO: 9)

or a variant thereof having at least 80% identity to SEQ ID NO: 9. In some embodiments, the

variant of SEQ ID NO: 9 has at least 85% identity, at least 86% identity, at least 87%

identity, at least 88% identity, at least 89% identity, at least 90% identity, at least 91%

identity, at least 92% identity, at least 93% identity, at least 94% identity, at least 95%

35 identity, at least 96%, at least 97%, at least 98% or at least 99% identity to SEQ ID NO: 9. In

some embodiments, the amylin analogue comprises an amino acid sequence with 100%

identity to SEQ ID NO: 9. SEQ ID NO: 9 may be considered the reference sequence for variants of the amylin analogue amino acid sequence.

In preferred embodiments, the amylin analogue is:

5 [19CD]-isoGlu-RD()
 LSSTEVGSNT-Hyp-NH₂ (SEQ ID NO: 2).

wherein:

() after amino acid symbols indicate residues whose side chains participate in an intramolecular lactam bridge,
 10 Gly(Me) is N-methylglycine [also known as sarcosine (Sar)],
 Ile(Me) is N-methylisoleucine,
 Aad is 2-aminoadipic acid, e.g. (2S)-2-aminoadipic acid [also (2S)-2-aminohexanedioic acid], also known as homo-glutamic acid,
 Hyp is 4-hydroxyproline, e.g. (2S,4R)-4-hydroxyproline [also denoted (4R)-4-hydroxy-
 15 L-proline], and
 [19CD]-isoGlu- is a 19-carboxy-nonadecanoyl group [19CD] covalently attached via an amide linkage to the alpha amino group of an isoGlu linker, wherein the side chain carboxyl group of the isoGlu linker is covalently attached via an amide linkage to the backbone nitrogen of the Arg residue at position X1 of the amylin analogue's peptide
 20 sequence Z (as described below);
 or a pharmaceutically acceptable salt or solvate thereof.

Parentheses “()” shown after the symbols for particular amino acid residues indicate residues whose side chains participate in an intramolecular lactam bridge. Thus, the amylin
 25 analogue compound present in the formulations of the invention has an intramolecular lactam bridge between the side chains of the residues at position X2 (such as aspartic acid, D) and at position X7 (such as lysine, K) as indicated by parentheses.

The amylin analogue of SEQ ID NO: 2 may also be referred to as ZP8396 or petrelintide.
 30 ZP8396 is also described in detail in WO 2018/046719 (which is incorporated herein by reference), wherein it is also referred to as “compound 35”.

In preferred embodiments, the amylin analogue is petrelintide, which has the formula:
 [19CD]-isoGlu-RD()
 35 Hyp-NH₂ (SEQ ID NO: 2)

wherein an intramolecular lactam bridge is formed between the side chains of residues indicated by parentheses "()"; and wherein [19CD]-isoGlu is a 19-carboxynonadecanoyl group covalently attached to the alpha amino group of an iso-glutamic acid linker; or a pharmaceutically acceptable salt thereof.

- 5 The amylin analogue may be in the form of a pharmaceutically acceptable salt or solvate, such as a pharmaceutically acceptable acid addition salt. The amylin analogue may be in the form of a pharmaceutically acceptable chloride salt. Any reference herein to "an amylin analogue" also encompasses pharmaceutically acceptable salts of the amylin analogue.
- 10 Amylin analogues may suitably be manufactured by standard synthetic methods. Thus, the peptides may be synthesized by, for example, methods comprising synthesizing the peptide by standard solid-phase or liquid-phase methodology, either stepwise or by fragment assembly, and optionally isolating and purifying the final peptide product. The method typically further comprises the step of forming an amide bond between the side chains at
- 15 positions 2 and 7. In the case of solid phase synthesis, cyclisation may be performed *in situ* on the solid phase (e.g. resin), i.e. before removal of the peptide from the solid phase.

Half-life extending moieties M

- As described herein, the N-terminal moiety R¹ in an amylin analogue of the invention may be
- 20 a half-life extending moiety M (sometimes referred to in the literature as, *inter alia*, a duration enhancing moiety or albumin binding moiety), optionally linked (covalently attached) to the peptide moiety Z via a linker moiety L. Among suitable half-life extending moieties are certain types of lipophilic substituents. Without wishing to be bound by any particular theory, it is thought that such lipophilic substituents (and other classes of half-life extending
- 25 moieties) bind albumin in the blood stream, thereby shielding the compound of the invention from renal filtration as well as enzymatic degradation and thus possibly enhancing the half-life of the compound *in vivo*. The lipophilic substituent may also modulate the potency of the compound as an agonist to the amylin (calcitonin) receptor.
- 30 The lipophilic substituent may be attached to the N-terminal amino acid residue or to the linker L via an ester, a sulfonyl ester, a thioester, an amide, an amine or a sulfonamide. Accordingly, it will be understood that preferably the lipophilic substituent includes an acyl group, a sulfonyl group, an N atom, an O atom or an S atom which forms part of the ester, sulfonyl ester, thioester, amide, amine or sulfonamide. Preferably, an acyl
- 35 group in the lipophilic substituent forms part of an amide or ester with the amino acid residue or the linker.

The lipophilic substituent may comprise a hydrocarbon chain having from 10 to 24 C atoms, e.g. from 14 to 22 C atoms, e.g. from 16 to 20 C atoms. Preferably it has at least 14 C atoms, and preferably has 20 C atoms or fewer. For example, the hydrocarbon chain may contain 14, 15, 16, 17, 18, 19 or 20 carbon atoms. The hydrocarbon chain may be linear or
5 branched, and may be saturated or unsaturated. Furthermore, it can include a functional group at the end of the hydrocarbon chain, e.g. a carboxylic acid group which may or may not be protected during synthesis. From the discussion above it will also be understood that the hydrocarbon chain is preferably substituted with a moiety which forms part of the attachment to the N-terminal amino acid residue of the peptide moiety Z or to the linker L, for
10 example an acyl group, a sulfonyl group, an N atom, an O atom or an S atom.

Most preferably, the hydrocarbon chain is substituted with an acyl group, and accordingly the hydrocarbon chain may be part of an alkanoyl group, for example a dodecanoyl, 2-butyloctanoyl, tetradecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl or
15 eicosanoyl group. Examples of functionalized hydrocarbon chains are 15-carboxypentadecanoyl, 17-carboxy-heptadecanoyl and 19-carboxy-nonadecanoyl.

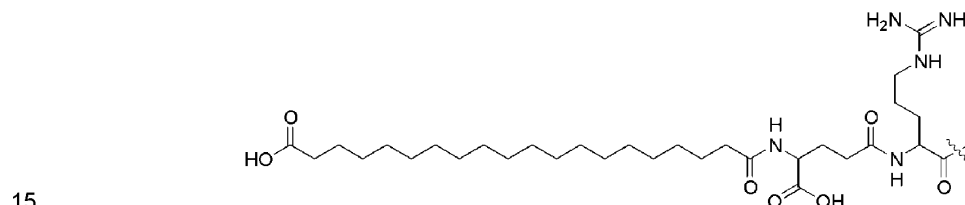
As mentioned above, a lipophilic substituent M may be linked to the N-terminal amino acid residue of Z via a linker L. In embodiments, the linker moiety L may itself comprise one, two,
20 three or more linked sub-moieties L^1 , L^2 , L^3 etc. When the linker L comprises only one such moiety, it is attached to the lipophilic substituent and to the N-terminal amino acid residue of Z. The linker may then be attached to the lipophilic substituent and to the N-terminal amino acid residue of Z independently by means of an ester, a sulfonyl ester, a thioester, an amide, an amine or a sulfonamide bond. Accordingly, it may include two moieties independently
25 selected from acyl, sulfonyl, an N atom, an O atom and an S atom. The linker may consist of a linear or branched C_{1-10} hydrocarbon chain or more preferably a linear C_{1-5} hydrocarbon chain. Furthermore, the linker can be substituted with one or more substituents selected from C_{1-6} alkyl, amino C_{1-6} alkyl, hydroxy C_{1-6} alkyl and carboxy C_{1-6} alkyl.

30 In some embodiments the linker may comprise one or more (e.g. one, two or three) linked amino acid residues, which may each independently be a residue of any naturally occurring or non-naturally occurring amino acid. For example, the linker may comprise one, two or three linked amino acid residues, each of which may independently be a residue of Gly, Pro, Ala, Val, Leu, Ile, Met, Cys, Phe, Tyr, Trp, His, Lys, Arg, Gln, Asn, α -Glu, γ -Glu, ϵ -Lys, Asp,
35 β -Asp, Ser, Thr, Gaba, Aib, β -Ala (i.e. 3-aminopropanoyl), 4-aminobutanoyl, 5-aminopentanoyl, 6-aminohexanoyl, 7-aminoheptanoyl, 8-aminooctanoyl, 9-aminononanoyl, 10-aminodecanoyl or 8Ado (i.e. 8-amino-3,6-dioxaoctanoyl).

References to γ -Glu, ϵ -Lys, and β -Asp indicate residues of amino acids which participate in bonds via their side chain carboxyl or amine functional groups. Thus γ -Glu, and β -Asp participate in bonds via their alpha amino and side chain carboxyl groups, while ϵ -Lys
 5 participates via its carboxyl and side chain amino groups. In the context of the present invention, γ -Glu and isoGlu are used interchangeably.

In certain embodiments, the linker comprises or consists of one, two or three independently selected residues of Glu, γ -Glu, ϵ -Lys, β -Ala, 4-aminobutanoyl, 8-aminooctanoyl or 8Ado.
 10 Linkers consisting of isoGlu and isoGlu-isoGlu may be particularly preferred.

An example of a lipophilic substituent comprising a lipophilic moiety M and linker L is shown in the formula below:

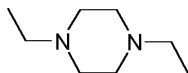


Here, the backbone nitrogen of an Arg residue (present at position X1 of the amylin analogue's peptide sequence Z) is covalently attached to the side chain carboxyl group of a Glu moiety via an amide linkage. A 19-carboxy-nonadecanoyl group is covalently attached to
 20 the alpha amino group of the Glu linker via an amide linkage. Thus the Glu linker is in an iso-Glu (or γ -Glu) configuration. This combination of lipophilic moiety and linker, attached to an Arg residue, may be referred to by the shorthand notation [19CD]-isoGlu-R, e.g. when shown in formulae of specific compounds.

25 The skilled person will be well aware of suitable techniques for preparing the compounds employed in the context of the invention. For examples of suitable chemistry, see, e.g., WO98/08871, WO00/55184, WO00/55119, Madsen et al (*J. Med. Chem.* 2007, 50, 6126-32), and Knudsen et al. 2000 (*J. Med Chem.* 43, 1664-1669).

30 The hydrocarbon chain in a lipophilic substituent may be further substituted. For example, it may be further substituted with up to three substituents selected from NH_2 , OH and COOH . If the hydrocarbon chain is further substituted, it is preferably further substituted with only

one substituent. Alternatively or additionally, the hydrocarbon chain may include a cycloalkane or heterocycloalkane moiety, for example as shown below:



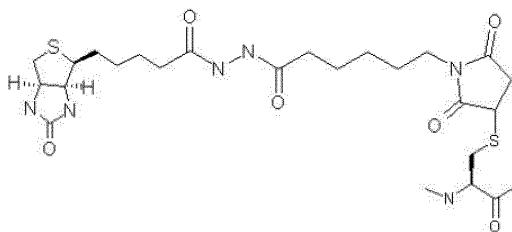
5

In some embodiments, the cycloalkane or heterocycloalkane moiety is a six-membered ring, e.g. a piperidine ring.

In alternative embodiments of the present invention, the N-terminal amino acid of Z in a compound of the invention may be linked (covalently attached) to a biotinylc substituent, optionally via a linker moiety L. Without wishing to be bound by any particular theory, it is likewise believed that such biotinylc substituents bind to albumin in the blood stream, thereby shielding the compound of the invention from enzymatic degradation and thus possibly enhancing the half-life of the compound *in vivo*. A linker, when present, may provide spacing between the peptide moiety Z and the biotinylc substituent.

The biotinylc substituent may be attached to the N-terminal amino acid residue or to the linker via an maleimide ester bond, a sulfonyl ester bond, a thioester bond, an amide bond, an amine bond or a sulfonamide bond. Accordingly, it will be understood that the biotinylc substituent preferably comprises an maleimido group, an acyl group, a sulfonyl group, an N atom, an O atom or an S atom which forms part of the ester, sulfonyl ester, thioester, amide, amine or sulfonamide bond in question.

Examples of biotinylc substituents may include



25

Biotin is known as Vitamin H or Coenzyme R, and is a water-soluble B-complex vitamin (vitamin B7). It has been shown to increase oral uptake of certain drugs.

Amylin receptor agonist activity

As described herein, an amylin analogue is a molecule that is an amylin receptor agonist, i.e. the molecule is capable of binding to, and inducing signaling by, one or more receptors or receptor complexes regarded as physiological receptors for human amylin.

5

Physiological receptors for human amylin include the human calcitonin receptor hCT-R, as well as complexes comprising the human calcitonin receptor hCT-R and at least one of the human receptor activity modifying proteins designated hRAMP1, hRAMP2 and hRAMP3. Complexes between hCT-R and hRAMP1, hRAMP2 and hRAMP3 are designated hAMYR1, hAMYR2 and hAMYR3 (i.e. human amylin receptors 1, 2 and 3) respectively. A compound may be considered an amylin receptor agonist if it has agonist activity at one or more of hAMYR1, hAMYR2 and hAMYR3, e.g. against hAMYR1 and/or hAMYR3, e.g. at hAMYR3.

10

Typically, an amylin receptor agonist will also have agonist activity at hCT-R when expressed in the absence of hRAMP1, hRAMP2 and hRAMP3. Typically, the agonist will have activity at hCT-R (when expressed in the absence of hRAMP1, hRAMP2 and hRAMP3) which is less than 10-fold higher than its activity at any one of hAMYR1, hAMYR2 and hAMYR3 (i.e. its activity at all of these receptors) in a comparable assay. Agonist activity at hCT-R may be less than 5-fold higher than agonist activity at hAMYR1, hAMYR2 and hAMYR3, substantially equal to (e.g. +/- 10%) agonist activity at hAMYR1, hAMYR2 and hAMYR3, or less than agonist activity at hAMYR1, hAMYR2 and hAMYR3. In this regard, it may be sufficient just to compare activity between hCT-R and hAMYR3.

15

20

The ability to induce cAMP formation (i.e. to induce adenylate cyclase activity) as a result of binding to the relevant receptor or receptor complex is typically regarded as indicative of agonist activity. Other intracellular signaling pathways or events may also be used as read-outs for amylin receptor agonist activity. These may include calcium release, β -arrestin recruitment, receptor internalization, kinase activation or inactivation, lipase activation, inositol phosphate release, diacylglycerol release or nuclear transcription factor translocation.

25

30

A suitable comparable assay format would utilize cells which express hCT-R and which differ only in their expression of hRAMP1, 2 and 3. For example, a "base" cell line which does not express any of hCT-R, hRAMP1, hRAMP2 and hRAMP3 may be engineered to generate cells which express (i) hCT-R, and (ii) one of hAMYR1, hAMYR2 and hAMYR3 (i.e. hCT-R plus one of hRAMP1, hRAMP2 and hRAMP3), e.g. hAMYR3. The base cells will typically be mammalian cells and may be primate cells. They may be non-human primate cells.

35

Preferably the base cell does not express any of CT-R, RAMP1, RAMP2 or RAMP3 (whether human, or native to the base cell if the base cell is non-human). The base cells may be fibroblast cells. Suitable non-human fibroblast base cells include COS7 cells, from African green monkey, which do not express native CT-R or RAMPs.

5

Comparative activity may be measured by any suitable means, such as via determination of EC₅₀ values as described below. It will be apparent that the same biological read-out must be for both receptor types.

- 10 Compounds of the present invention may exhibit a number of advantageous properties in relation to human amylin and existing analogues thereof, such as pramlintide, IAPP-GI, and analogues described in WO2012/168430, WO2012/168431 and WO2012/168432. As compared to human amylin or any of those analogues, compounds of the invention may, for example, exhibit improved efficacy (e.g., in the form of improved *in vitro* activity or potency at
- 15 one or more of the receptors hCT-R, hAMYR1, hAMYR2 or hAMYR3. Additionally, or alternatively, compounds of the invention may exhibit improved solubility in aqueous media, especially at pH values in the range from 4 to 7.5, or at a range of pH values across that range. Moreover, compounds of the present invention may additionally or alternatively exhibit reduced tendency to undergo fibrillation in pharmaceutically relevant aqueous media,
- 20 especially at pH values in the range from 4 to 7, or at a range of pH values across that range. Furthermore, compounds of the present invention may additionally or alternatively exhibit improved chemical stability (i.e. reduced tendency to undergo chemical degradation) in aqueous media, especially at pH values in the range from 4 to 9, or at a range of pH values across that range.

25

Compounds of the invention may thus be well suited for formulation in acidic media (e.g. pH 4) and in neutral or near-neutral media (e.g. pH 7 or 7.4), in contrast to pramlintide, for example, which generally exhibits poor chemical stability and rapid fibrillation in pharmaceutically relevant aqueous media at neutral pH.

30

- In general, it is preferred to use a biological assay which measures intracellular signalling caused by binding of the compound to the relevant receptor, as discussed above. Activation of the calcitonin/amylin receptor by compounds of the invention (which behave as agonists of the receptor) induces cAMP formation and activation of other intracellular signaling
- 35 pathways and events. Thus, production of cAMP or any other suitable parameter in suitable cells expressing the receptor can be used to monitor agonist activity towards the receptor.

The skilled person will be aware of suitable assay formats, and examples are provided below. For example, the assays may make use of the human calcitonin receptor (hCT-R, e.g. isoform 2 of the hCT-R) or the hAMYR3 receptor (see the examples below). Where sequences of precursor proteins are referred to, it should be understood that assays may
5 make use of the mature protein, lacking the signal sequence.

EC₅₀ values may be used as a numerical measure of agonist potency at a given receptor. An EC₅₀ value is a measure of the concentration of a compound required to achieve half of that compound's maximal activity in a particular assay. Thus, for example, a compound
10 having EC₅₀ [hCT-R] lower than the EC₅₀ [hCT-R] of native human amylin, or lower than that of pramlintide, in a particular assay may be considered to have higher potency or activity at the receptor than native human amylin, or higher than that of pramlintide, respectively.

In some embodiments of compounds of the present invention, the EC₅₀ towards hCT-R is
15 below about 1.5 nM (e.g. 0.001 to 1.5 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hCT-R is below about 0.9 nM (e.g. 0.001 to 0.9 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hCT-R is below about 0.5 nM (e.g. 0.001 to 0.5 nM).

20 In some embodiments of compounds of the present invention, the EC₅₀ towards hCT-R is below about 0.3 nM (e.g. 0.001 to 0.3 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hCT-R is below about 0.2 nM (e.g. 0.001 to 0.2 nM).

25 The EC₅₀ at hCT-R may be an indication of the effect of a compound on food intake, weight gain and/or weight loss. Compounds with lower EC₅₀ values at hCT-R may have a greater effect on these parameters.

In some embodiments of compounds of the present invention, the EC₅₀ towards hAMYR3 is
30 below about 1.0 nM (e.g. 0.001 to 1.0 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hAMYR3 is below about 0.5 nM (e.g. 0.001 to 0.5 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hAMYR3 is below about 0.4 nM (e.g. 0.001 to 0.4 nM).

35 In some embodiments of compounds of the present invention, the EC₅₀ towards hAMYR3 is below about 0.3 nM (e.g. 0.001 to 0.3 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hAMYR3 is below about 0.2 nM (e.g. 0.001 to 0.2 nM).

The EC₅₀ at hCT-R (when expressed in the absence of hRAMP1, hRAMP2 and hRAMP3)
5 may be less than the EC₅₀ at any or all of hAMYR1, hAMYR2 and hAMYR3, e.g. at hAMYR3.

For example, the EC₅₀ at hCT-R (when expressed in the absence of hRAMP1, hRAMP2 and hRAMP3) may be less than 10-fold lower than the EC₅₀ at any or all of hAMYR1, hAMYR2
10 and hAMYR3, e.g. at hAMYR3.

The EC₅₀ at hCT-R (when expressed in the absence of hRAMP1, hRAMP2 and hRAMP3) may be less than 5-fold lower than the EC₅₀ at any or all of hAMYR1, hAMYR2 and hAMYR3, e.g. at hAMYR3.
15

The EC₅₀ at hCT-R (when expressed in the absence of hRAMP1, hRAMP2 and hRAMP3) may be substantially equal to (e.g. +/- 50%) the EC₅₀ at any or all of hAMYR1, hAMYR2 and hAMYR3, e.g. at hAMYR3.

20 The EC₅₀ at hCT-R (when expressed in the absence of hRAMP1, hRAMP2 and hRAMP3) may be higher than the EC₅₀ at any or all of hAMYR1, hAMYR2 and hAMYR3, e.g. at hAMYR3.

GIPR / GLP-1R dual agonists

25 A GIPR / GLP-1R dual agonist is a molecule which has agonist activity at both the gastric inhibitory polypeptide receptor (GIPR) and the glucagon-like peptide-1 receptor (GLP-1R). In other words, a GIPR / GLP-1R dual agonist is capable of binding to, and inducing signaling by, both GIPR and GLP-1R. Thus, a GIPR / GLP-1R dual agonist has activities of both GIP and GLP-1. The term "dual agonist" is synonymous with "co-agonist". GIPR / GLP-1R dual
30 agonists may be referred to as "compounds", "peptides" or "dual agonists" herein.

The GIPR / GLP-1R dual agonist may be in the form of a pharmaceutically acceptable salt or solvate, such as a pharmaceutically acceptable acid addition salt. Any reference herein to "a GIPR / GLP-1R dual agonist" also encompasses pharmaceutically acceptable salts of the
35 GIPR / GLP-1R dual agonist.

The GIPR / GLP-1R dual agonist may be any GIPR / GLP-1R dual agonist known in the art, such as any of those described in WO 2011/119657, WO 2013/164483 and WO 2014/192284.

- 5 In some embodiments, the GIPR / GLP-1R dual agonist comprises the amino acid sequence Y[Aib]EGTFTSDYSI[Aib]LDKIAQKAFVQWLIAGGPSSGAPPPS (SEQ ID NO: 10) or a variant thereof having at least 80% identity to SEQ ID NO: 10. In some embodiments, the variant of SEQ ID NO: 10 has at least 85% identity, at least 86% identity, at least 87% identity, at least 88% identity, at least 89% identity, at least 90% identity, at least 91% identity, at least 92% identity, at least 93% identity, at least 94% identity, at least 95% identity, at least 96%, at least 97%, at least 98% or at least 99% identity to SEQ ID NO: 10. In some embodiments, the GIPR / GLP-1R dual agonist comprises an amino acid sequence with 100% identity to SEQ ID NO: 10. SEQ ID NO: 10 may be considered the reference sequence for variants of the GIPR / GLP-1R dual agonist amino acid sequence.

15

Tirzepatide

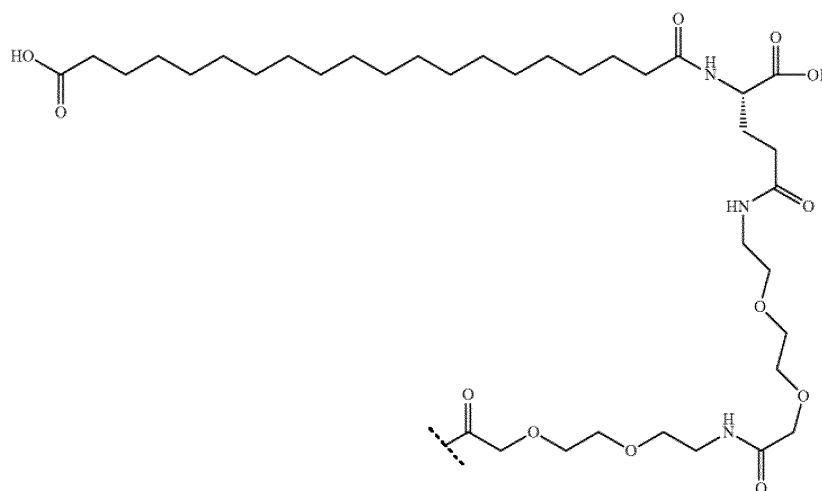
- In preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide, or a pharmaceutically acceptable salt or solvate thereof. Tirzepatide (described in WO 2016/111971) is also known as LY3298176 or GIP/GLP-1 RA, and is sold under the brand name Mounjaro and Zepbound.

- Tirzepatide is a peptide comprising an amidated C-terminus and a fatty acid moiety conjugated to the side-chain of the lysine at position 20 via a linker. More specifically, tirzepatide has the following structure:
- 25 Hy-Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]AFVQWLIAGGPSSGAPPPS-NH₂ (SEQ ID NO: 4)
- wherein
- [Aib] is α-aminoisobutyric acid, and
- [K] is lysine with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)₁-CO-(CH₂)₁₈-COOH
- 30 conjugated to the epsilon-amino group of the lysine side-chain.

- Thus, in some embodiments, the GIPR / GLP-1R dual agonist is
- Hy-Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]AFVQWLIAGGPSSGAPPPS-NH₂ (SEQ ID NO: 4)
- 35 wherein
- [Aib] is α-aminoisobutyric acid, and

[K] is lysine with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)₁-CO-(CH₂)₁₈-COOH conjugated to the epsilon-amino group of the lysine side-chain (tirzepatide); or a pharmaceutically acceptable salt or solvate thereof.

- 5 The lysine at position 20 of tirzepatide is conjugated to a fatty acid moiety via a linker. The linker is (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)₁ and the fatty acid moiety is -CO-(CH₂)₁₈-CO₂H (i.e. 19-carboxynonadecanoyl). Together, the linker and lipid moiety are referred to as (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)₁-CO-(CH₂)₁₈-COOH, which has the following chemical structure:



10

wherein the dotted line intersects the bond linking to the nitrogen atom of the epsilon-amino group of the lysine at position 20 of the peptide portion of tirzepatide.

- 15 The structure of tirzepatide is depicted in Figure 5 using a combination of chemical structure notation and one-letter amino acid code.

In some embodiments, the GIPR / GLP-1R dual agonist is a compound of the formula:

Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]A-X-VQWLIAGGPSSGAPPPS (SEQ ID NO: 3)

20

wherein:

[Aib] is α-aminoisobutyric acid, and

[K] is lysine with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)_a-CO-(CH₂)_b-COOH conjugated to the epsilon-amino group of the lysine side-chain,

a is 1 or 2, b is 10 to 20,

25

X is Phe or 1-Nal,

and the C-terminal amino acid is optionally amidated as a C-terminal primary amide;

or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the C-terminal amino acid is amidated as a C-terminal primary amide. In some embodiments, X is Phe. In some embodiments, a is 1. In some
5 embodiments, b is 16 to 18. In some embodiments, b is 16 or 18. In some embodiments, b is 18.

GIPR / GLP-1R dual agonist activity

The GIPR / GLP-1R dual agonist has at least one GIP biological activity and at least one
10 GLP-1 biological activity. The GIPR / GLP-1R dual agonist has agonist activity at GIPR and GLP-1R receptors, e.g. human GIPR and GLP-1R.

Whether a given compound has GIPR agonist activity and/or GLP-1R agonist activity may be tested using assays known in the art, such as the assays described in WO 2013/164483,
15 WO 2014/192284 and WO 2016/111971.

For example, the ability of a given compound to bind GIPR and GLP-1R (i.e. the affinity of the compound for the receptors) may be measured using an *in vitro* binding assay and expressed as a dissociation constant (K_d).
20

Preferably, GIPR and GLP-1R agonism by a given compound may be measured using an *in vitro* functional assay, such as measuring signaling from GIPR and GLP-1R expressed in cells and stimulated with the compound. Signaling may be quantified by measuring, for example, changes in cellular cAMP levels. EC_{50} values for *in vitro* receptor agonist activity
25 may be used as a numerical measure of agonist activity / potency at a given receptor. An EC_{50} value is a measure of the concentration (e.g. mol/L) of a compound required to achieve half of that compound's maximal activity in a particular assay. A compound having a numerical EC_{50} at a particular receptor which is lower than the EC_{50} of a reference compound in the same assay may be considered to have higher potency at that receptor
30 than the reference compound.

GIP activity

In some embodiments, the dual agonist has an EC_{50} at the GIP receptor (e.g. the human GIP receptor) which is below about 2.0 nM, below about 1.5 nM, below about 1.0 nM, below
35 about 0.9 nM, below about 0.8 nM, below about 0.7 nM, below about 0.6 nM, below about 0.5 nM, below about 0.4 nM, below about 0.3 nM, below about 0.2 nM, below about 0.1 nM, below about 0.09 nM, below about 0.08 nM, below about 0.07 nM, below about 0.06 nM,

below about 0.05 nM, below about 0.04 nM, below about 0.03 nM, below about 0.02 nM, or below about 0.01 nM, e.g. when assessed using the GIP receptor activity assay as described in WO 2013/164483.

- 5 In some embodiments, the dual agonist has an EC_{50} at the GIP receptor which is between about 0.005 and about 2.0 nM, between about 0.01 nM and about 2.0 nM, between about 0.025 and about 2.0 nM, between about 0.005 and about 1.5 nM, between about 0.01 nM and about 1.5 nM, between about 0.025 and about 1.5 nM, between about 0.005 and about 1.0 nM, between about 0.01 nM and about 1.0 nM, between about 0.025 and about 1.0 nM,
- 10 between about 0.005 and about 0.5 nM, between about 0.01 nM and about 0.5 nM, between about 0.025 and about 0.5 nM, between about 0.005 and about 0.25 nM, between about 0.01 nM and about 0.25 nM, between about 0.025 and about 0.25 nM, e.g. when assessed using the GIP receptor activity assay as described in WO 2013/164483.
- 15 An alternative measure of GIPR agonist activity may be derived by comparing the potency of a dual agonist with the potency of a known (or reference) GIPR agonist when both are measured in the same assay. Thus the relative potency at GIPR may be defined as:
[EC_{50} (reference agonist)] / [EC_{50} (dual agonist)].
- 20 Thus a value of 1 indicates that the dual agonist and reference agonist have equal potency, a value of >1 indicates that the dual agonist has higher potency (i.e. lower EC_{50}) than the reference agonist, and a value of <1 indicates that the dual agonist has lower potency (i.e. higher EC_{50}) than the reference agonist.
- 25 The reference GIP agonist may be, for example, human GIP. Typically the relative potency will be between about 0.001 and about 100, e.g. between about 0.001 and about 10, between about 0.001 and about 5, between about 0.001 and about 1, between about 0.001 and about 0.5, between about 0.001 and about 0.1, between about 0.001 and about 0.05, or between about 0.001 and about 0.01; between about 0.01 and about 10, between about
- 30 0.01 and about 5, between about 0.01 and about 1, between about 0.01 and about 0.5, between about 0.01 and about 0.1, or between about 0.01 and about 0.05; between about 0.05 and about 10, between about 0.05 and about 5, between about 0.05 and about 1, between about 0.05 and about 0.5, or between about 0.05 and about 0.1; between about 0.1 and about 10, between about 0.1 and about 5, between about 0.1 and about 1, or between
- 35 about 0.1 and about 0.5; between about 0.5 and about 10, between about 0.5 and about 5, or between about 0.5 and about 1; between about 1 and about 10, or between about 1 and about 5; or between about 5 and about 10.

GLP-1 activity

In some embodiments, the dual agonist has an EC₅₀ at the GLP-1 receptor (e.g. the human GLP-1 receptor) which is below about 2.0 nM, below about 1.5 nM, below about 1.0 nM, below about 0.9 nM, below about 0.8 nM, below about 0.7 nM, below about 0.6 nM, below about 0.5 nM, below about 0.4 nM, below about 0.3 nM, below about 0.2 nM, below about 0.1 nM, below about 0.09 nM, below about 0.08 nM, below about 0.07 nM, below about 0.06 nM, below about 0.05 nM, below about 0.04 nM, e.g. when assessed using a GLP-1 receptor potency assay as described in PCT/EP2022/074420.

In some embodiments, the dual agonist has an EC₅₀ at the GLP-1 receptor which is between about 0.005 and about 2.5 nM, between about 0.01 nM and about 2.5 nM, between about 0.025 and about 2.5 nM, between about 0.005 and about 2.0 nM, between about 0.01 nM and about 2.0 nM, between about 0.025 and about 2.0 nM, between about 0.005 and about 1.5 nM, between about 0.01 nM and about 1.5 nM, between about 0.025 and about 1.5 nM, between about 0.005 and about 1.0 nM, between about 0.01 nM and about 1.0 nM, between about 0.025 and about 1.0 nM, between about 0.005 and about 0.5 nM, between about 0.01 nM and about 0.5 nM, between about 0.025 and about 0.5 nM, between about 0.005 and about 0.25 nM, between about 0.01 nM and about 0.25 nM, between about 0.025 and about 0.25 nM, e.g. when assessed using the GLP-1 receptor potency assay as described in PCT/EP2022/074420.

An alternative measure of GLP-1 agonist activity may be derived by comparing the potency of a dual agonist with the potency of a known (or reference) GLP-1 agonist when both are measured in the same assay. Thus, the relative potency at the GLP-1 receptor may be defined as:

$$[EC_{50}(\text{reference agonist})] / [EC_{50}(\text{dual agonist})].$$

Thus, a value of 1 indicates that the dual agonist and reference agonist have equal potency, a value of >1 indicates that the dual agonist has higher potency (i.e. lower EC₅₀) than the reference agonist, and a value of <1 indicates that the dual agonist has lower potency (i.e. higher EC₅₀) than the reference agonist.

The reference GLP-1 agonist may, for example, be human GLP-1(7-37), liraglutide (NN2211; Victoza), or Exendin-4, but is preferably liraglutide.

Typically the relative potency will be between about 0.001 and about 100, e.g. between about 0.001 and about 10, between about 0.001 and about 5, between about 0.001 and about 1, between about 0.001 and about 0.5, between about 0.001 and about 0.1, between about 0.001 and about 0.05, or between about 0.001 and about 0.01; between about 0.01 and about 10, between about 0.01 and about 5, between about 0.01 and about 1, between about 0.01 and about 0.5, between about 0.01 and about 0.1, or between about 0.01 and about 0.05; between about 0.05 and about 10, between about 0.05 and about 5, between about 0.05 and about 1, between about 0.05 and about 0.5, or between about 0.05 and about 0.1; between about 0.1 and about 10, between about 0.1 and about 5, between about 0.1 and about 1, or between about 0.1 and about 0.5; between about 0.5 and about 10, between about 0.5 and about 5, or between about 0.5 and about 1; between about 1 and about 10, or between about 1 and about 5; or between about 5 and about 10.

The dual agonists described in the examples below have slightly lower GLP-1 potency than liraglutide and so may, for example, have a relative potency between about 0.01 and about 1, between about 0.01 and about 0.5 or between about 0.01 and about 0.1.

It will be understood that the absolute potencies of the dual agonists at each receptor are much less important than the balance between the GIP and GLP-1 agonist activities. Thus, it is perfectly acceptable for the absolute GIP or GLP-1 potency to be lower than that of known agonists at those receptors, as long as the dual agonist compound exerts acceptable relative levels of potency at both receptors. Any apparent deficiency in absolute potency can be compensated by an increased dose if required.

GIPR / GLP-1R dual agonists used in the present invention may display a balanced GIP and GLP-1 activity. "Balanced GIPR and GLP-1R activity" refers to a compound that has affinity for GIPR and GLP-1R in an *in vitro* binding assay at a molar ratio that is close to 1:1, such as 1:1 GIPR/GLP-1R, 2:1 GIPR/GLP-1R, 3:2 GIPR/GLP-1R, 1:2 GIPR/GLP-1R, or 2:3 GIPR/GLP-1R.

GIPR / GLP-1R dual agonists used in the present invention may display selectivity for GIP and GLP-1 receptors versus receptors for glucagon and GLP-2. The term "selectivity" or "selective against" when used herein to reference GIP and GLP-1 activity in comparison to glucagon activity, refers to a compound that displays 1000-, 500-, or about 100-fold higher potency for GIP and GLP-1 over glucagon when the data is normalized from the respective *in vitro* binding assays. The term "selectivity" or "selective against" when used herein to reference GIP and GLP-1 activity in comparison to GLP-2 activity, refers to a compound that

displays 250-, 200-, 100-, or about 50-fold higher potency for GIP and GLP-1 over GLP-2 when the data is normalized from the respective *in vitro* functional assays.

Therapeutic uses

5 In a broad aspect, the invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in therapy. The invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in treating or preventing a disease in a subject. The invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of treating or preventing a disease in a subject. The invention provides the combination of an amylin
10 analogue and a GIPR / GLP-1R dual agonist for use in a method of treating or preventing a disease in a subject. The invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of treating or preventing a disease in a subject, wherein the method comprises administering to the subject the amylin analogue and the GIPR / GLP-1R dual agonist.

15

In other words, the invention provides use of an amylin analogue and a GIP / GLP-1R dual agonist in preparation of a medicament for treating or preventing a disease in a subject.

Alternatively expressed, the invention provides the combination of an amylin analogue and a
20 GIPR / GLP-1R dual agonist for use in therapy. The invention provides the combination of an amylin analogue and a GIPR / GLP-1R dual agonist for use in treating or preventing a disease in a subject. The invention provides the combination of an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of treating or preventing a disease in a subject. The invention provides the combination of an amylin analogue and a GIPR / GLP-
25 1R dual agonist for use in a method of treating or preventing a disease in a subject, wherein the method comprises administering to the subject the amylin analogue and the GIPR / GLP-1R dual agonist.

The invention provides use of a combination of an amylin analogue and a GIP / GLP-1R dual
30 agonist in preparation of a medicament for treating or preventing a disease in a subject.

The invention may be alternatively expressed as a method of treatment. Thus, the invention provides a method of treating or preventing a disease in a subject, the method comprising administering to the subject an amylin analogue and a GIPR / GLP-1R dual agonist.

35

Methods and uses of the present invention may be carried out *in vitro*, *in vivo*, or *ex vivo*.

The term "treatment" (as well as "treating" and other grammatical variants thereof) as employed in the context of the invention refers to an approach for obtaining beneficial or desired clinical results. For the purposes of the present invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilization of (i.e. not worsening of) state of disease, delay or slowing of disease progression, amelioration or palliation of disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" may also refer to prolongation of survival compared to expected survival in the absence of treatment.

"Treatment" is an intervention performed with the intention of preventing the development of, or altering the pathology of, a disorder. Accordingly, "treatment" refers both to therapeutic treatment and to prophylactic or preventative measures. As used in the context of prophylactic or preventative measures, the pharmaceutical formulation need not completely prevent the development of the disease or disorder. Those in need of treatment include those already suffering from the disorder, as well as those in which development of the disorder is to be prevented. "Treatment" also means inhibition or reduction of an increase in pathology or symptoms (e.g. weight gain or hypoglycaemia) compared to the absence of treatment, and is not necessarily meant to imply complete cessation of the relevant condition.

The terms "disease", "disorder" and "condition" are synonymous and are used interchangeably herein to refer to a state of malfunction of the body. The term "disease" thus encompasses "disorder" and "condition".

In the context of the invention, the disease to be treated or prevented is any disease related to excess body weight. Thus, the invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in treating or preventing a disease in a subject, wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes. Diabetes may be type 1 diabetes or type 2 diabetes. In other words, the invention provides a method of treating or preventing a disease in a subject, the method comprising administering to the subject an amylin analogue and a GIPR / GLP-1R dual agonist, wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes.

In some embodiments, the disease is overweight. In some embodiments, the disease is obesity. In some embodiments, the disease is morbid obesity. In some embodiments, the disease is diabetes. In some embodiments, the disease is type 1 diabetes. In some embodiments, the disease is type 2 diabetes. In some embodiments, the disease is a disease linked to obesity or to diabetes.

The body weight of a subject may be referred to using Body Mass Index (BMI), which is calculated for human subjects by dividing the weight of the subject in kilograms by the square of the height of the subject in metres.

5

In some embodiments, the subject is obese. In some embodiments, the subject has a BMI of 30.0 to 39.9 kg/m² corresponding to obese.

10 In some embodiments, the subject is morbidly obese. In some embodiments, the subject has a BMI of 40.0 kg/m² or higher corresponding to morbidly obese.

In some embodiments, the disease linked to obesity or to diabetes is selected from the group consisting of obesity-linked inflammation, obesity-linked gallbladder disease, obesity-induced sleep apnea, obesity-linked respiratory problems, degeneration of cartilage, osteoarthritis, infertility, Alzheimer's disease, pre-diabetes, gestational diabetes, insulin resistance syndrome, inadequate glucose control, impaired glucose tolerance (IGT), disease states associated with elevated blood glucose levels, metabolic disease, metabolic syndrome, hyperglycemia, hypertension, dyslipidaemia, atherogenic dyslipidemia, kidney failure, arteriosclerosis, atherosclerosis, macrovascular disease, microvascular disease, diabetic heart disease, diabetic cardiomyopathy, heart failure as a diabetic complication, coronary heart disease, peripheral artery disease and stroke.

25 The compounds of the invention may also be useful in lowering circulating LDL levels and/or increasing HDL/LDL ratio.

25

The effects of the compounds of the invention may be mediated in whole or in part via an effect on body weight, or may be independent thereof.

Metabolic syndrome is characterized by a group of metabolic risk factors in one person. They include abdominal obesity (excessive fat tissue around the abdominal internal organs), atherogenic dyslipidemia (blood fat disorders including high triglycerides, low HDL cholesterol and/or high LDL cholesterol, which foster plaque buildup in artery walls), elevated blood pressure (hypertension), insulin resistance and glucose intolerance, prothrombotic state (e.g. high fibrinogen or plasminogen activator inhibitor-1 in the blood), and proinflammatory state (e.g., elevated C-reactive protein in the blood).

35

Individuals with metabolic syndrome are at increased risk of coronary heart disease and other diseases related to other manifestations of arteriosclerosis (e.g. stroke and peripheral vascular disease). The dominant underlying risk factor for this syndrome appears to be abdominal obesity.

5

Obesity is linked with low grade inflammation (sometimes designated "obesity-linked inflammation"). It is also generally recognised that obesity (along with other syndromes) causes an increased vascular permeability which allows pathogens and toxins such as LPS to enter the cell wall of the intestinal tract and thereby initiate inflammation. The changes that result from the inflammatory response are essentially the same regardless of the cause and regardless of where the insult arises. The inflammatory response may be acute (short lived) or chronic (longer lasting).

10

The dual agonist activity of the GIPR / GLP-1R dual agonists described herein may be particularly beneficial in many of the conditions described, as the two activities may complement one another.

15

For example, malabsorption is a condition arising from abnormality in the absorption of water and/or food nutrients, such as amino acids, sugars, fats, vitamins or minerals, via the gastrointestinal (GI) tract, leading to malnutrition and/or dehydration. Malabsorption may be a result of physical (e.g. traumatic) or chemical damage to the intestinal tract. Dual agonists as described in this specification may be capable of improving intestinal barrier function, reducing gastric emptying, and increasing intestinal absorption while at the same time normalising intestinal transit time. This would not only help patients to increase the absorption of nutrients and liquid, but would also alleviate patients' social problems related to meal-stimulated bowel movements.

20

25

Furthermore, intestinal function and metabolic disorders may be closely inter-related, with each contributing to the development or symptoms of the other.

30

Reducing body weight

The invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of inhibiting weight gain and/or reducing body weight in a subject.

Alternatively expressed, the invention provides a combination of an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of inhibiting weight gain and/or reducing body weight in a subject.

35

In other words, the invention provides a method of inhibiting weight gain and/or reducing body weight in a subject, wherein the method comprises administering an amylin analogue and a GIPR / GLP-1R dual agonist to the subject.

5

Alternatively expressed, the invention provides a method of inhibiting weight gain and/or reducing body weight in a subject, wherein the method comprises administering a combination of an amylin analogue and a GIPR / GLP-1R dual agonist to the subject.

“Inhibiting weight gain” may also be referred to as “reducing weight gain”. “Reducing body weight” may also be referred to as “promoting weight loss”.

The amylin analogue and GIPR / GLP-1R dual agonist may increase or prolong the feeling of satiation experienced by a subject, thereby reducing the appetite of the subject, leading to reduced food intake. Thus, the invention may be expressed as an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of reducing food intake and/or reducing appetite.

The amylin analogue and GIPR / GLP-1R dual agonist of the invention may be used for therapeutic or cosmetic purposes. Thus, the inhibition of weight gain or reduction of body weight of the subject may be cosmetic (i.e. non-therapeutic). Effects of the compounds of the invention on body weight may be therapeutic or cosmetic.

Thus, the invention provides a non-therapeutic method of inhibiting weight gain and/or reducing body weight in a subject, wherein the method comprises administering an amylin analogue and a GIPR / GLP-1R dual agonist to the subject. The invention provides a cosmetic method of inhibiting weight gain and/or reducing body weight in a subject, wherein the method comprises administering an amylin analogue and a GIPR / GLP-1R dual agonist to the subject.

Such non-therapeutic methods aim to reduce body weight of subjects that are not obese or morbidly obese.

In some embodiments of the non-therapeutic methods of the invention, the subject is of a healthy weight. In other words, in some embodiments, the subject is not overweight, not obese and not morbidly obese. In some embodiments, the subject has a BMI of 18.5 to 24.9 kg/m² corresponding to healthy weight.

In some embodiments of the non-therapeutic methods of the invention, the subject is overweight. In other words, in some embodiments, the subject is not of a healthy weight, but is not obese and not morbidly obese. In some embodiments, the subject has a BMI of 25.0 to 29.9 kg/m² corresponding to overweight.

5

The invention further relates to an amylin analogue and GIPR / GLP-1R dual agonist for use in methods that are not directed towards treating disease *per se*. Such uses and methods may be considered preventative of disease in so far as they may be utilised prior to the onset of disease (e.g. pre diagnosis) e.g. to ameliorate unwanted physiological

10 characteristics or alter certain physiological parameters. Furthermore, such uses or methods may be considered cosmetic.

The effects of the compounds described above may be mediated in whole or in part via an effect on body weight, or may be independent thereof. Independently of their effect on body

15 weight, the compounds of the invention may have a beneficial effect on glucose tolerance and/or glucose control.

In some embodiments, the subject exhibits a reduction in body weight upon treatment with the amylin analogue and GIPR / GLP-1R dual agonist. In some embodiments, the subject

20 exhibits a reduction in body weight of at least 1%, such as at least 5%, at least 10%, at least 15%, at least 20%, at least 22.5% or at least 25%, compared to their body weight before treatment. In some embodiments, the subject exhibits a reduction in body weight of at least 0.5% per month (i.e. 0.5% reduction in body weight at the end of each month compared to body weight at the start of the month), such as at least 0.75% per month, at least 1% per

25 month, at least 1.25% per month or at least 1.3% per month. In some embodiments, the subject exhibits a reduction in body weight of 0.5% per month, 0.75% per month, 1% per month, 1.25% per month or 1.3% per month.

Methods of increasing weight loss

30 The invention also provides a method of increasing weight loss in a subject in need thereof, the method comprising:

(i) providing a subject undergoing treatment with a GIPR / GLP-1R dual agonist as described herein for a period of time during which weight loss in the subject plateaus and/or the subject is or becomes resistant to the GIPR / GLP-1R dual agonist, and

35 (ii) following step (i), administering to the subject (a) the GIPR / GLP-1R agonist and (b) an amylin analogue as described herein, each in an amount that together is sufficient to increase weight loss in the subject.

The invention also provides method of increasing weight loss in a subject in need thereof, the method comprising:

- (i) providing a subject who fails to respond to treatment with a GIPR / GLP-1R dual agonist as described herein, and
- (ii) administering to the subject (a) the GIPR / GLP-1R dual agonist and (b) an amylin analogue as described herein, each in an amount that together is sufficient to increase weight loss in the subject.

The invention also provides a method of increasing weight loss in a subject in need thereof, the method comprising:

- (i) providing a subject undergoing treatment with a GIPR / GLP-1R dual agonist as described herein for a period of at least 1 month, and
- (ii) following step (i), administering to the subject (a) the GIPR / GLP-1R dual agonist and (b) an amylin analogue as described herein, each in an amount that together is sufficient to increase weight loss in the subject.

The invention also provides a method of maintaining weight loss in a subject in need thereof, the method comprising:

- (i) providing a subject undergoing treatment with a GIPR / GLP-1R dual agonist as described herein, wherein the subject has experienced weight loss, and
- (ii) following step (i), administering to the subject (a) the GIPR / GLP-1R dual agonist and (b) an amylin analogue as described herein, each in an amount that together is sufficient to maintain the weight loss in the subject.

The invention also provides a method of increasing weight loss in a subject in need thereof, the method comprising:

- (i) providing a subject undergoing treatment with a GIPR / GLP-1R dual agonist as described herein for a period of time during which weight loss in the subject plateaus and/or the subject is or becomes resistant to the GIPR / GLP-1R dual agonist and there is a need to achieve additional weight loss in the subject, and
- (ii) following step (i), administering to the subject (a) the GIPR / GLP-1R dual agonist and (b) an amylin analogue as described herein, each in an amount that together is sufficient to achieve the additional weight loss in the subject.

The invention also provides a method of achieving additional weight loss in a subject in need thereof, the method comprising:

(i) providing a subject undergoing treatment with a GIPR / GLP-1R dual agonist as described herein for a period of time during which weight loss is achieved and there is a need to achieve additional weight loss in the subject, and

(ii) following step (i), administering to the subject (a) the GIPR / GLP-1R dual agonist
5 and (b) an amylin analogue as described herein, each in an amount that together is sufficient to achieve the additional weight loss in the subject.

As described elsewhere herein, preferably the amylin analogue is petrelintide. Preferably the GIPR / GLP-1R dual agonist is tirzepatide. Most preferably, the amylin analogue is
10 petrelintide and the GIPR / GLP-1R dual agonist is tirzepatide.

Mode of administration

The administration to a subject of the amylin analogue and GIPR / GLP-1R dual agonists described herein may be by any mode of administration common or standard in the art, e.g.
15 oral, intravenous, intramuscular, subcutaneous, sublingual, intranasal, intradermal, suppository routes or implanting. In preferred embodiments, administration is by subcutaneous injection.

In some embodiments, the amylin analogue is administered to the subject via injection. In
20 some embodiments, the amylin analogue is administered to the subject via subcutaneous injection. The amylin analogue may be in any form suitable for administration to a subject. Preferably, the amylin analogue is in a form suitable for subcutaneous (s/c or s.c.) administration to a subject.

25 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject via injection. In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject via subcutaneous injection. The GIPR / GLP-1R dual agonist may be in any form suitable for administration to a subject. Preferably, the GIPR / GLP-1R dual agonist is in a form suitable for subcutaneous (s/c or s.c.) administration to a subject.

30 In some embodiments, both the amylin analogue and the GIPR / GLP-1R dual agonist are administered to the subject via injection, preferably via subcutaneous injection.

In preferred embodiments, the amylin analogue is
35 [19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-Hyp-NH₂ (SEQ ID NO: 2)

or a pharmaceutically acceptable salt or solvate thereof, and is administered to the subject via subcutaneous injection. In preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject via subcutaneous injection.

5

In some embodiments, the subject is a human subject.

In some embodiments, the subject is suffering from a disease or disorder described herein.

In some embodiments, the subject is overweight, has obesity, has morbid obesity, has
10 diabetes, or has a disease linked to obesity or to diabetes. In some embodiments, the subject is not suffering from a disease or disorder described herein. In some embodiments, the subject is at risk of developing a disease or disorder described herein.

Dose

15 Herein, the term "dose" refers to the quantity of a given compound (amylin analogue or GIPR / GLP-1R dual agonist) administered to a subject at each administration event. The term "dosage" refers to both the quantity and frequency at which a given compound is administered to a subject.

20 The dose of the amylin analogue and the dose of the GIPR / GLP-1R dual agonist may be independently selected. Any dose of amylin analogue described herein may be combined with any dose of GIPR / GLP-1R dual agonist described herein.

In the context of the invention, the subject is administered a therapeutically effective amount
25 of the amylin analogue and a therapeutically effective amount of the GIPR / GLP-1R dual agonist. The amylin analogue is administered to the subject in a therapeutically effective amount. The GIPR / GLP-1R dual agonist is administered to the subject in a therapeutically effective amount. Both the amylin analogue and the GIPR / GLP-1R dual agonist are administered to the subject in a therapeutically effective amount.

30

The exact dose of amylin analogue or GIPR / GLP-1R dual agonist administered to a subject may depend on, *inter alia*, the nature and severity of the disease or disorder to be treated, on the sex, age, body weight and general condition of the subject to be treated, on possible
35 other, concomitant, disease or disorder that is undergoing or is to undergo treatment, as well as on other factors that will be known to a medical practitioner of skill in the art.

Dose of amylin analogue

In some embodiments, the amylin analogue is administered to the subject at a dose of up to about 10 mg, such as up to about 9.5 mg, up to about 9 mg, up to about 8.5 mg, up to about 8 mg, up to about 7.5 mg, up to about 7 mg, up to about 6.5 mg, up to about 6 mg, up to about 5.5 mg, up to about 5 mg, up to about 4.5 mg, up to about 4 mg, up to about 3.5 mg, up to about 3 mg, up to about 2.5 mg, up to about 2 mg, up to about 1.5 mg, up to about 1 mg, up to about 0.5 mg, or up to about 0.25 mg.

In some embodiments, the amylin analogue is administered to the subject at a dose of from about 0.04 mg to about 10 mg, such as about 0.04 mg to about 7 mg, about 0.04 mg to about 6 mg, about 0.04 mg to about 4.4 mg, or about 0.04 mg to about 2.4 mg.

In some embodiments, the amylin analogue is administered to the subject at a dose of from about 0.6 mg to about 10 mg, about 0.6 mg to about 7 mg, about 0.6 mg to about 6 mg, about 0.6 mg to about 4.4 mg, or about 0.6 mg to about 2.4 mg.

In some embodiments, the amylin analogue is administered to the subject at a dose of from about 0.7 mg to about 10 mg, about 0.7 mg to about 7 mg, about 0.7 mg to about 6 mg, about 0.7 mg to about 4.4 mg, or about 0.7 mg to about 2.4 mg,

In some embodiments, the amylin analogue is administered to the subject at a dose of about 0.5 mg to about 10.0 mg, preferably about 0.6 mg to about 7.5 mg, preferably about 1.2 mg to about 7.5 mg, preferably about 1.2 to about 6.0 mg, preferably about 2.4 to about 6.0 mg, preferably about 2.4 to about 4.0 mg, preferably about 2.4 to about 3.5 mg.

In some embodiments, the amylin analogue is administered to the subject at a dose of about 10 mg, such as about 9.5 mg, about 9 mg, about 8.5 mg, about 8 mg, about 7.5 mg, about 7 mg, about 6.5 mg, about 6 mg, about 5.5 mg, about 5 mg, about 4.5 mg, about 4.4 mg, about 4 mg, about 3.5 mg, about 3.4 mg, about 3 mg, about 2.5 mg, about 2.4 mg, about 2 mg, about 1.5 mg, about 1.4 mg, about 1 mg, about 0.5 mg, about 0.35 mg, about 0.25 mg, about 0.16 mg, about 0.08 mg, or about 0.04mg.

In some embodiments, the amylin analogue is administered to the subject at a dose of from about 0.0001 to about 1 mg/kg body weight, such as from about 0.0005 to about 1 mg/kg body weight, about 0.001 to about 1 mg/kg body weight, about 0.01 to about 1 mg/kg body weight, about 0.1 to about 1 mg/kg body weight, about 0.2 to about 1 mg/kg body weight,

about 0.3 to about 1 mg/kg body weight, about 0.4 to about 1 mg/kg body weight, or about 0.5 to about 1 mg/kg body weight.

5 In some embodiments, the amylin analogue is administered to the subject at a dose of from about 0.0001 to about 0.5 mg/kg body weight, such as from about 0.0005 to about 0.5 mg/kg body weight, about 0.001 to about 0.5 mg/kg body weight, about 0.01 to about 0.5 mg/kg body weight, about 0.1 to about 0.5 mg/kg body weight, about 0.2 to about 0.5 mg/kg body weight, about 0.3 to about 0.5 mg/kg body weight, or about 0.4 to about 0.5 mg/kg body weight.

10

In some embodiments, the amylin analogue is administered to the subject at a dose of from about 0.0001 to about 0.15 mg/kg body weight, such as from about 0.0005 to about 0.15 mg/kg body weight, about 0.001 to about 0.15 mg/kg body weight, or about 0.01 to about 0.15 mg/kg body weight.

15

In some embodiments, the amylin analogue is administered to the subject at a dose of from about 0.0001 to about 0.1 mg/kg body weight, such as from about 0.0005 to about 0.1 mg/kg body weight, about 0.001 to about 0.1 mg/kg body weight, or about 0.01 to about 0.1 mg/kg body weight.

20

In some embodiments, the amylin analogue is administered to the subject at a dose of from about 10 nmol/kg body weight to about 500 nmol/kg body weight, such as from about 10 to about 100 nmol/kg body weight, or about 10 to about 50 nmol/kg body weight. In some embodiments, the amylin analogue is administered to the subject at a dose of about 10, 50 or 100 nmol/kg body weight.

25

In some embodiments, the dose of amylin analogue is not the same during each administration. In some embodiments, the dose of amylin analogue is increased for each successive administration. In some embodiments, the dose of amylin analogue is increased for each successive administration until a desired maximum dose is reached. Optionally, the desired maximum dose may be maintained over a given time period (i.e. the dose plateaus). In some embodiments, the dose of amylin analogue is the same during each administration.

30

Preferably, the amylin analogue is

35 [19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-Hyp-NH₂ (SEQ ID NO: 2),

or a pharmaceutically acceptable salt or solvate thereof, and is administered to the subject at any of the doses described herein.

Dose of GIPR / GLP-1R dual agonist

5 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of up to about 15 mg, up to about 12.5 mg, up to about 10 mg, up to about 7.5 mg, up to about 5 mg, up to about 2.5 mg, up to about 2 mg, or up to about 1 mg.

10 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of from about 1 mg to about 15 mg, from about 2.5 mg to about 15 mg, from about 5 mg to about 15 mg, from about 7.5 mg to about 15 mg, from about 10 mg to about 15 mg, or from about 12.5 mg to about 15 mg.

15 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of from about 0.5 mg to about 10 mg, about 1 mg to about 10 mg, from about 2.5 mg to about 10 mg, from about 5 mg to about 10 mg, or from about 7.5 mg to about 10 mg.

In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of from about 1 mg to about 5 mg, or from about 2.5 mg to about 5 mg.

20 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of about 15 mg, about 12.5 mg, about 10 mg, about 7.5 mg, about 5 mg, about 2.5 mg, or about 1 mg. In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of about 15 mg, about 10 mg or about 5 mg.

25 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of from about 0.0001 to about 1 mg/kg body weight, such as from about 0.0005 to about 1 mg/kg body weight, about 0.001 to about 1 mg/kg body weight, about 0.01 to about 1 mg/kg body weight, about 0.1 to about 1 mg/kg body weight, about 0.2 to about 1 mg/kg body weight, about 0.3 to about 1 mg/kg body weight, about 0.4 to about 1 mg/kg body weight, or about 0.5 to about 1 mg/kg body weight.

30 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of from about 0.0001 to about 0.5 mg/kg body weight, such as from about 0.0005 to about 0.5 mg/kg body weight, about 0.001 to about 0.5 mg/kg body weight, about 0.01 to about 0.5 mg/kg body weight, about 0.1 to about 0.5 mg/kg body weight, about 0.2 to about

0.5 mg/kg body weight, about 0.3 to about 0.5 mg/kg body weight, or about 0.4 to about 0.5 mg/kg body weight.

In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a
5 dose of from about 0.0001 to about 0.15 mg/kg body weight, such as from about 0.0005 to about 0.15 mg/kg body weight, about 0.001 to about 0.15 mg/kg body weight, or about 0.01 to about 0.15 mg/kg body weight.

In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a
10 dose of from about 0.0001 to about 0.1 mg/kg body weight, such as from about 0.0005 to about 0.1 mg/kg body weight, about 0.001 to about 0.1 mg/kg body weight, or about 0.01 to about 0.1 mg/kg body weight.

In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a
15 dose of from about 1 nmol/kg body weight to about 100 nmol/kg body weight, such as from about 1 to about 50 nmol/kg body weight, or about 1 to about 10 nmol/kg body weight. In some embodiments, the amylin analogue is administered to the subject at a dose of about 1, 5 or 10 nmol/kg body weight.

20 In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of from about 5 mg/mL to about 30 mg/mL. In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject at a dose of about 5 mg/mL, about 10 mg/mL, about 15 mg/mL, about 20 mg/mL, about 25 mg/mL or about 30 mg/mL.

25 Preferably, the GIPR / GLP-1R dual agonist is:

Hy-Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]AFVQWLIAGGPSSGAPPPS-NH₂ (SEQ ID NO: 4)

wherein [K] is lysine with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)₁-CO-(CH₂)₁₈-COOH conjugated to the epsilon-amino group of the lysine side-chain
30 (tirzepatide);

or a pharmaceutically acceptable salt or solvate thereof, and is administered to the subject at any of the doses described herein.

In preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide or a
35 pharmaceutically acceptable salt or solvate thereof, and is administered to the subject at a dose of about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg or about 15 mg.

Timing of administration

The amylin analogue and/or the GIPR / GLP-1R dual agonist may be administered to the subject a certain number of times "daily" or a certain number of times "a day". "A day" is
5 intended to mean approximately 24 hours, for example, approximately 20, 21, 22, 23, 24, 25, 26, 27 or 28 hours.

The amylin analogue and/or the GIPR / GLP-1R dual agonist may be administered to the subject a certain number of times "weekly" a certain number of times "a week". A "week" is
10 intended to mean approximately 7 days, for example, approximately 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 or 9 days with each "day" being counted as approximately a 24 hour period.

As will be appreciated in the art, the time between doses may be varied to some extent so that each and every dose is not separated by precisely the same time (i.e. not precisely a
15 day or precisely a week). This will often be directed under the discretion of the physician. Thus, doses may be separated in time by a clinically acceptable range of times.

Thus, in some embodiments, the reference to "day" may mean 24 hours $\pm$ 8 hours. That is to say the administration may take place either up to and including about eight hours before, or
20 up to and including about eight hours after the stated time.

In some embodiments, the reference to "week" may mean 7 days $\pm$ 2 days. That is to say the administration may take place either up to and including about two days before, or up to and including about two days after the stated day. As such, the administration may take place
25 about 2 days or about 1 day before, or about 1 day or about 2 days after, the stated day. Hence, the administration may take place 2 days or 1 day before, or 1 day or 2 days after, the stated day.

Timing for amylin analogue

30 The amylin analogue may be administered continuously (e.g. by intravenous administration or another continuous drug administration method).

In some embodiments, the amylin analogue is administered at intervals. In some embodiments, the amylin analogue is administered at regular intervals.
35

In some embodiments, the amylin analogue is administered to the subject at least about once a day (i.e., at least about once daily). In some embodiments, the amylin analogue is

administered to the subject once a day, once every two days, once every three days, once every four days, once every five days, or once every six days. In some embodiments, the amylin analogue is administered to the subject once a week, once every two weeks, once every three weeks, or once every four weeks. In some embodiments, the amylin analogue is
5 administered to the subject once a month.

In some embodiments, the amylin analogue is administered to the subject twice a day, twice a week, or twice a month.

10 In some embodiments, the amylin analogue is administered to the subject every other day (i.e. once every two days).

In preferred embodiments, the amylin analogue is administered to the subject once a week (i.e. once every week or once weekly). In preferred embodiments, the amylin analogue is
15 SEQ ID NO: 2 or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject once a week (i.e. once weekly).

Timing for GIPR /GLP-1R dual agonist

The GIPR / GLP-1R dual agonist may be administered continuously (e.g. by intravenous
20 administration or another continuous drug administration method).

In some embodiments, the GIPR / GLP-1R dual agonist is administered at intervals. In some embodiments, the GIPR / GLP-1R dual agonist is administered at regular intervals.

25 In some embodiments, the amylin analogue is administered to the subject at least about once a day (i.e., at least about once daily). In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject once a day, once every two days, once every three days, once every four days, once every five days, or once every six days. In some
30 embodiments, the GIPR / GLP-1R dual agonist is administered to the subject once a week, once every two weeks, once every three weeks, or once every four weeks. In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject once a month.

In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject twice a day, twice a week, or twice a month.

35 For some preferred embodiments, the GIPR / GLP-1R dual agonist is administered to the subject once a week (i.e. once weekly). In preferred embodiments, the GIPR / GLP-1R dual

agonist is tirzepatide or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject once a week (i.e. once weekly).

Timing of administration of both compounds

- 5 The present invention encompasses, but is not limited to, medical uses and methods of treatment wherein the amylin analogue and the GIPR / GLP-1R dual agonist are administered to the subject simultaneously. The amylin analogue and the GIPR / GLP-1R dual agonist may be administered to the subject at different time-points, following different dosage regimes (i.e. timings). For example, the amylin analogue may be administered daily
10 whilst the GIPR / GLP-1R dual agonist is administered weekly. The amylin analogue and the GIPR / GLP-1R dual agonist may be administered at different times on the same day.

- The invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of treating or preventing a disease in a subject, wherein the method comprises
15 administering to the subject the amylin analogue and the GIPR / GLP-1R dual agonist at different times or at the same time. Thus, in some embodiments, the amylin analogue and the GIPR / GLP-1R dual agonist are administered to the subject at different times. In some embodiments, the amylin analogue and the GIPR / GLP-1R dual agonist are administered to the subject at the same time.

- 20 The invention provides an amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of treating or preventing a disease in a subject, wherein the method comprises administering to the subject the amylin analogue and the GIPR / GLP-1R dual agonist separately or together. In some embodiments, the amylin analogue and the GIPR / GLP-1R
25 dual agonist are administered to the subject separately. In some embodiments, the amylin analogue and the GIPR / GLP-1R dual agonist are administered to the subject together.

- In some embodiments, the amylin analogue and the GIPR / GLP-1R dual agonist are administered to the subject at different intervals. In some embodiments, the amylin analogue
30 and the GIPR / GLP-1R dual agonist are administered to the subject at the same interval.

Administration period

- The term "administration period" may be used herein to refer to the total period in which the amylin analogue or the GIPR / GLP-1R dual agonist is administered to the subject. In other
35 words, the administration period is the period starting with the first administration event (i.e. the first time the compound is administered to the subject) and ending with the final administration event (i.e. the final time the compound is administered to the subject).

Alternatively expressed, the administration period is the period in which subject is treated with the compound.

5 In some embodiments, the amylin analogue is administered to the subject for at least one month (i.e. the administration period for the amylin analogue is at least one month). In some embodiments, the amylin analogue is administered to the subject for at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, or at least twelve months.

10

In some embodiments, the amylin analogue is administered to the subject for at least one year (i.e. the administration period for the amylin analogue is at least one year). In some embodiments, the amylin analogue is administered to the subject for at least two years, at least three years, at least four years, at least five years, at least six years, at least seven
15 years, at least eight years, at least nine years, or at least ten years.

In some embodiments, the amylin analogue is administered to the subject for more than ten years. In some embodiments, the amylin analogue is administered to the subject indefinitely. In some embodiments, the amylin analogue is administered to the subject for the rest of the
20 subject's life.

In some embodiments, the GIPR / GLP-1 dual agonist is administered to the subject for at least one month (i.e. the administration period for the GIPR / GLP-1 dual agonist is at least one month). In some embodiments, the GIPR / GLP-1 dual agonist is administered to the
25 subject for at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, or at least twelve months.

In some embodiments, the GIPR / GLP-1 dual agonist is administered to the subject for at least one year (i.e. the administration period for the GIPR / GLP-1 dual agonist is at least one year). In some embodiments, the GIPR / GLP-1 dual agonist is administered to the
30 subject for at least two years, at least three years, at least four years, at least five years, at least six years, at least years, at least eight years, at least nine years, or at least ten years.

35 In some embodiments, the GIPR / GLP-1 dual agonist is administered to the subject for more than ten years. In some embodiments, the GIPR / GLP-1 dual agonist is administered

to the subject indefinitely. In some embodiments, the GIPR / GLP-1 dual agonist is administered to the subject for the rest of the subject's life.

Administration period of both compounds

5 The invention does not require that administration of the amylin analogue and the GIPR / GLP-1R dual agonist begin or end at the same time. In other words, the amylin analogue and the GIPR / GLP-1R dual agonist may have different administration periods. The present invention thus concerns a period in which administration to a subject of the amylin analogue overlaps with administration to the subject of the GIPR / GLP-1R dual agonist.

10

In some embodiments, the administration period for the amylin analogue begins at the same time as the administration period for the GIPR / GLP-1R dual agonist. In other words, administration to the subject of the amylin analogue and the GIPR / GLP-1R dual agonist begins at the same time.

15

In some embodiments, the administration period for the amylin analogue begins before the administration period for the GIPR / GLP-1R dual agonist. In other words, the amylin analogue is being administered to the subject, and then the GIPR / GLP-1R dual agonist begins to be administered to the subject. Alternatively expressed, a subject undergoing treatment with the amylin analogue begins to be additionally treated with the GIPR / GLP-1R dual agonist.

In preferred embodiments, the administration period for the GIPR / GLP-1R dual agonist begins before the administration period for the amylin analogue. In other words, the GIPR / GLP-1R dual agonist is being administered to the subject, and then the amylin analogue begins to be administered to the subject. Alternatively expressed, a subject undergoing treatment with the GIPR / GLP-1R dual agonist begins to be additionally treated with the amylin analogue.

30 In particularly preferred embodiments, tirzepatide or a pharmaceutically acceptable salt or solvate thereof is being administered to the subject, and then the amylin analogue begins to be administered to the subject, wherein the amylin analogue is:

[19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-
LSSTEVGST-Hyp-NH₂ (SEQ ID NO: 2)

35 or a pharmaceutically acceptable salt or solvate thereof. In other words, the subject is undergoing treatment with tirzepatide, and then treatment with the specific amylin analogue defined in the previous sentence is added on top of the tirzepatide treatment.

Titration regime

In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject according to a titration regimen.

5

In some embodiments, the amylin analogue is administered to the subject according to a titration regimen.

10 A titration regimen comprises an initial set of one or more administrations of the dual agonist in a "titration period" followed by a set of one or more administrations of the dual agonist in a "treatment period". Typically, the dose of the dual agonist at each administration in the titration period is lower than the dose at each administration in the treatment period.

15 A first purpose of the titration period is to acclimatize the patient to side-effects of the dual agonist. Initial administration of the dual agonist may produce side-effects which decrease in severity after further administrations as the patient adapts. Administering the dual agonist at a lower dose in the titration period may curtail the initial severity of these side-effects. A second purpose of the titration period may be to determine an appropriate dose for the dual agonist for the patient. The dose of the dual agonist may be increased across the titration
20 period, allowing a physician to observe side-effects at different doses and thereby determine an appropriate dose for treatment.

Thus, in some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject one or more times at a first dose, and thereafter one or more times at a second dose. In
25 some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject one or more times at additional doses (i.e. at a third dose, fourth dose, fifth dose etc.). In some embodiments, the GIPR / GLP-1R dual agonist is administered to the subject one or more times at a third, fourth, fifth or sixth dose.

30 Each dose of the GIPR / GLP-1R dual agonist may be administered any number of times. In some embodiments, each dose of the GIPR / GLP-1R dual agonist is administered a number of times independently selected from one time, two times, three times, four times, five times, six times, seven times, eight times, nine times and ten times.

35 Each dose of the dual agonist may be any of the doses of dual agonist described elsewhere herein.

Thus, in some embodiments, the amylin analogue is administered to the subject one or more times at a first dose, and thereafter one or more times at a second dose. In some embodiments, the amylin analogue is administered to the subject one or more times at additional doses (i.e. at a third dose, fourth dose, fifth dose etc.). In some embodiments, the amylin analogue is administered to the subject one or more times at a third, fourth, fifth or sixth dose.

Each dose of the amylin analogue may be administered any number of times. In some embodiments, each dose of the amylin analogue is administered a number of times independently selected from one time, two times, three times, four times, five times, six times, seven times, eight times, nine times and ten times.

Each dose of the amylin analogue may be any of the doses of amylin analogue described elsewhere herein.

The timing of each administration may be any of the timings of administration described elsewhere herein. In preferred embodiments, each administration of the GIPR / GLP-1R dual agonist is once weekly.

Advantageously, the subject may not experience nausea or vomiting (or other adverse gastrointestinal effects) during the titration period. This allows for a shorter or expedited titration period prior to administration of higher doses.

For tirzepatide, an initial titration dose of about 2.5 mg is recommended, administered once weekly for 4 weeks. After 4 weeks administration, the dose is increased to about 5 mg (which provides a therapeutic). However, if a stronger therapeutic effect is required, after at least 4 weeks administration at a dose of about 5 mg, the dose can be increased to about 7.5 mg. The dose of tirzepatide may be increased by increments of about 2.5 mg, with at least 4 weeks at each dose, in this manner, until a final therapeutic dose is identified, to a maximum dose of about 15 mg. Once a final therapeutic dose is identified, tirzepatide may continue to be administered indefinitely at that dose, or until treatment ceases.

Thus, in preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject at a dose of about 2.5 mg once weekly for 4 weeks, and thereafter at a dose of about 5 mg once weekly.

In preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject at a dose of about 2.5 mg once weekly for 4 weeks, thereafter at a dose of about 5 mg once weekly for at least 4 weeks, and thereafter at a dose of about 7.5 mg once weekly.

In preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject at a dose of about 2.5 mg once weekly for 4 weeks, thereafter at a dose of about 5 mg once weekly for at least 4 weeks, thereafter at a dose of about 7.5 mg once weekly for at least 4 weeks, and thereafter at a dose of about 10 mg once weekly.

In preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject at a dose of about 2.5 mg once weekly for 4 weeks, thereafter at a dose of about 5 mg once weekly for at least 4 weeks, thereafter at a dose of about 7.5 mg once weekly for at least 4 weeks, thereafter at a dose of about 10 mg once weekly for at least 4 weeks, and thereafter at a dose of about 12.5 mg once weekly.

In preferred embodiments, the GIPR / GLP-1R dual agonist is tirzepatide or a pharmaceutically acceptable salt or solvate thereof (as described elsewhere herein) and is administered to the subject at a dose of about 2.5 mg once weekly for 4 weeks, thereafter at a dose of about 5 mg once weekly for at least 4 weeks, thereafter at a dose of about 7.5 mg once weekly for at least 4 weeks, thereafter at a dose of about 10 mg once weekly for at least 4 weeks, thereafter at a dose of about 12.5 mg once weekly for at least 4 weeks, and thereafter at a dose of about 15 mg once weekly.

Pharmaceutical compositions

The amylin analogue and the GIPR / GLP-1R dual agonist may each be formulated as a pharmaceutical composition.

A pharmaceutical composition comprising an amylin analogue may be referred to as an "amylin analogue pharmaceutical composition" herein. Similarly, a pharmaceutical composition comprising a GIPR / GLP-1R dual agonist may be referred to as a "GIPR / GLP-1R dual agonist pharmaceutical composition" herein. This terminology differentiates the types of pharmaceutical compositions. The expressions "the pharmaceutical compositions" and "the pharmaceutical compositions of the invention" as used herein therefore encompass

amylin analogue pharmaceutical compositions and GIPR / GLP-1R dual agonist pharmaceutical compositions.

Thus, the invention provides a pharmaceutical composition comprising an amylin analogue
5 and a pharmaceutical composition comprising a GIPR / GLP-1R dual agonist for use in treating or preventing a disease in a subject, wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes.

In other words, the invention provides use of a pharmaceutical composition comprising an
10 amylin analogue and a pharmaceutical composition comprising a GIPR / GLP-1R dual agonist in preparation of a medicament for treating or preventing a disease in a subject, wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes.

15 The invention also provides a method of treating or preventing a disease in a subject, the method comprising administering to the subject a pharmaceutical composition comprising an amylin analogue and a pharmaceutical composition comprising a GIPR / GLP-1R dual agonist, wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes.

20 The invention also provides a pharmaceutical composition comprising an amylin analogue and a pharmaceutical composition comprising a GIPR / GLP-1R dual agonist for use in a method of inhibiting weight gain and/or reducing body weight in a subject.

25 The invention also provides a method of inhibiting weight gain and/or reducing body weight in a subject, wherein the method comprises administering a pharmaceutical composition comprising an amylin analogue and a pharmaceutical composition comprising a GIPR / GLP-1R dual agonist to the subject.

30 In a preferred aspect, the combination of the invention comprises the separate administration of the amylin analogue pharmaceutical composition and the GIPR /GLP-1R dual agonist pharmaceutical composition to a subject.

It will be understood that the amylin analogue and the GIPR / GLP-1R dual agonist when
35 formulated as a pharmaceutical composition may be in the form of a pharmaceutically acceptable salt or solvate, such as a pharmaceutically acceptable acid addition salt, as described elsewhere herein.

The pharmaceutical compositions may be suited for administration with or without storage.

5 The pharmaceutical compositions may comprise a therapeutically effective amount of the compound (i.e. the amylin analogue or GIPR / GLP-1R dual agonist).

The pharmaceutical compositions may comprise a carrier, excipient and/or vehicle. In other words, the compound is in admixture with a carrier, excipient, and/or vehicle. In some embodiments, the carrier is a pharmaceutically acceptable carrier.

10

The term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical carriers. Pharmaceutically acceptable carriers for therapeutic use are well known in the pharmaceutical art and are described, for example, in "Remington's Pharmaceutical Sciences", 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, 15 USA, 1985. For example, sterile saline and phosphate-buffered saline at slightly acidic or physiological pH may be used. Suitable pH-buffering agents may, e.g., be phosphate, citrate, acetate, tris(hydroxymethyl)aminomethane (TRIS), N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid (TAPS), ammonium bicarbonate, diethanolamine, histidine, arginine, lysine or acetate (e.g. as sodium acetate), or mixtures thereof. The term further 20 encompasses any carrier agents listed in the US Pharmacopeia for use in animals, including humans.

A pharmaceutical composition of the invention may be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active 25 component or components. The unit dosage form may be presented as a packaged preparation, the package containing discrete quantities of the preparation, for example, packaged tablets, capsules or powders in vials or ampoules. The unit dosage form may also be, e.g., a capsule, cachet or tablet in itself, or it may be an appropriate number of any of these packaged forms. A unit dosage form may also be provided in single-dose injectable 30 form, for example in the form of a pen device containing a liquid-phase (typically aqueous) composition. Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for e.g. oral, intravitreal, rectal, vaginal, nasal, topical, enteral or parenteral (including subcutaneous (sc), intramuscular (im), intravenous (iv), intradermal and 35 transdermal) administration or administration by inhalation. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods

well known in the art of pharmaceutical formulation. Subcutaneous or transdermal modes of administration may in some cases be suitable for compounds of the invention.

Further embodiments relate to devices, dosage forms and packages used to deliver the pharmaceutical formulations of the present invention. Thus, at least one peptide in a stable or preserved formulation or solution described herein can be administered to a patient in accordance with the present invention via a variety of delivery methods, including by sc or im injection, or by transdermal, pulmonary or transmucosal administration, or by implant, or by use of an osmotic pump, cartridge, micro-pump or other means recognized by a person of skill in the art.

The pharmaceutical compositions may be formulated as liquid suitable for administration by injection or infusion. In some embodiments, the pharmaceutical compositions of the invention are formulated as 1 mL solutions for injection. In some embodiments, the pharmaceutical compositions are formulated as 0.5 mL solutions for injection.

Still further embodiments relate to oral formulations and oral administration. Formulations for oral administration may rely on the co-administration of adjuvants (e.g. resorcinols and/or nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to artificially increase the permeability of the intestinal walls, and/or the co-administration of enzymatic inhibitors (e.g. pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) or trasylol) to inhibit enzymatic degradation. The active constituent compound of a solid-type dosage form for oral administration can be mixed with at least one additive, such as sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, alginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, or glyceride. These dosage forms can also contain other type(s) of additives, e.g. an inactive diluting agent, a lubricant (such as magnesium stearate), a paraben, a preserving agent (such as sorbic acid, ascorbic acid or alpha-tocopherol), an antioxidant (such as cysteine), a disintegrant, binder, thickener, buffering agent, pH-adjusting agent, sweetening agent, flavoring agent or perfuming agent.

The pharmaceutical compositions may comprise a tonicity agent. The pharmaceutical compositions may comprise a preservative.

In some embodiments, the pharmaceutical compositions comprise one or more additional active agents, such as one or more additional peptides.

Amylin analogue pharmaceutical compositions

In some embodiments, the amylin analogue is formulated as an amylin analogue pharmaceutical composition.

5

The amylin analogue pharmaceutical composition comprises the amylin analogue as described herein at any of the doses described herein.

10

In some embodiments, the amylin analogue pharmaceutical composition comprises a buffer at a concentration of from about 0.5 mM to 25 mM.

In some embodiments, the amylin analogue pharmaceutical composition has a pH of from about 5.8 to about 6.9.

15

In some embodiments, the amylin analogue pharmaceutical composition consists of the following components:

Component	Quantity/mL Drug product	Function
amylin analogue of SEQ ID NO: 2	4.0 mg	Active pharmaceutical ingredient
Trometamol/Tromethamine (TRIS)	2.42 mg	Buffer
Sodium chloride	6.9 mg	Tonicity agent
1M Hydrochloric acid	q.s.	pH adjustment
0.5 M Sodium hydroxide	q.s.	pH adjustment
Water for injection	Ad 1.0 mL	Solvent

GIPR / GLP-1R dual agonist pharmaceutical compositions

20

In some embodiments, the GIPR / GLP-1R dual agonist is formulated as a GIPR / GLP-1R dual agonist pharmaceutical composition.

The GIPR / GLP-1R dual agonist pharmaceutical composition comprises the GIPR / GLP-1R dual agonist as described herein at any of the doses described herein.

25

In some embodiments, the GIPR / GLP-1R dual agonist pharmaceutical composition comprises the following ingredients:

Component	Function
GIPR / GLP-1R dual agonist	Drug substance
Sodium phosphate (dibasic, heptahydrate)	Buffer
Hydrochloric acid	pH adjustment
Sodium Hydroxide	pH adjustment
Water for Injections	Solvent

- 5 Tirzepatide (under the product name Zepbound) is clinically formulated for subcutaneous injection as 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg tirzepatide in 0.5 mL solution with the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. The formulation has a pH of 6.5
10 to 7.5.

Thus, in some embodiments, the GIPR / GLP-1R dual agonist pharmaceutical composition comprises tirzepatide or a pharmaceutically acceptable salt or solvate thereof and sodium phosphate buffer.

15

In some embodiments, the GIPR / GLP-1R dual agonist pharmaceutical composition has a pH of 6.5 to 7.5.

Kits and devices

- 20 The invention provides a kit comprising an amylin analogue of the invention and a GIPR / GLP-1R dual agonist of the invention. The amylin analogue and GIPR / GLP-1R dual agonist in the kit of the invention may have any of the features of the amylin analogue and GIPR / GLP-1R dual agonist as described herein. In some embodiments, the kit further comprises packaging and/or instructions for use.

25

The invention also provides a device comprising an amylin analogue of the invention and a GIPR / GLP-1R dual agonist of the invention, for delivery to a subject. The amylin analogue and GIPR / GLP-1R dual agonist in the device of the invention may have any of the features of the amylin analogue and GIPR / GLP-1R dual agonist as described herein. Via such
30 devices, the amylin analogue and GIPR / GLP-1R dual agonist can be administered to a

subject via a variety of delivery methods, including: intravenous, subcutaneous, intramuscular or intraperitoneal injection; oral administration; transdermal administration; pulmonary or transmucosal administration; administration by implant, osmotic pump, cartridge or micro pump; or by other means recognized by a person of skill in the art.

5

Sequence listing

SEQ ID NO: 1 – Amylin analogue specifying possible amino acid substitutions

SEQ ID NO: 2 – Specific amylin analogue

SEQ ID NO: 3 – GIPR / GLP-1R dual agonist specifying possible amino acid substitutions

10

SEQ ID NO: 4 – Tirzepatide

SEQ ID NO: 5 – Amylin

SEQ ID NO: 6 – Pramlintide

SEQ ID NO: 7 – GLP-1

SEQ ID NO: 8 – Variant amylin analogue sequence

15

EXAMPLES

The following examples are provided to illustrate preferred aspects of the invention and are not intended to limit the scope of the invention.

20

Summary – Potent Weight Loss Effects of Amylin Analogue ZP8396 in Combination with Tirzepatide in DIO Rats25

Marketed hormone pharmacotherapies for treatment of obesity include liraglutide and semaglutide, which both are GLP-1R agonists.

30

Tirzepatide, a GIPR and GLP-1R dual agonist, is approved both for the treatment of type 2 diabetes (Mounjaro) and weight loss (Zepbound). Combination therapy consisting of hormone pharmacotherapies with complementary modes of action may add even further weight loss to that of liraglutide, semaglutide and tirzepatide without compromising safety and tolerability.

35

ZP8396, petrelintide, a novel amylin analog designed for once weekly dosing, has demonstrated the potential to reduce body weight and improve glycemia in rat models of obesity and diabetes. In this study we investigate the combined weight loss effects of ZP8396 and tirzepatide in diet-induced obese (DIO) rats.

DIO rats were treated for 2 weeks with either vehicle or tirzepatide 10 nmol/kg by once daily subcutaneous injection. From day 14 to day 34, vehicle-treated rats continued either on vehicle or were switched to ZP8396 10 nmol/kg, every 2nd day subcutaneous. Likewise, tirzepatide-treated rats continued either on tirzepatide or were switched to tirzepatide plus
5 ZP8396. The weight loss effects were assessed by measurement of body weight and food intake.

Combined treatment with ZP8396 (petrelintide) and tirzepatide achieved a significant, sustained, and greater reduction in cumulative food intake and a corresponding significant,
10 sustained and greater body weight reduction compared to vehicle- and each mono-treated group (-5,2% ± 0,7 ZP8396, -8,2% ± 1,1 tirzepatide, -15,3% ± 0,9 combination, 6.5% ± 0,4, vehicle; relative to initial body weights ± SEM). Exposure was determined for ZP8396 and tirzepatide, and was similar for each compound between comparative groups.

15 In conclusion, combining ZP8396 (petrelintide) and tirzepatide in DIO rats showed significantly greater body weight loss compared to the mono treatments. Combining ZP8396 and tirzepatide may potentially be a future therapy approach for weight management of people living with overweight and obesity.

20 **Example 1: Effects of GIPR / GLP-1R dual agonist alone and in combination with an amylin analogue in diet-induced obese rats**

This study was performed to assess the effect of treatment with an amylin analogue on top of treatment with GIPR / GLP-1R dual agonist tirzepatide in diet-induced obese (DIO) rats.

25

The amylin analogue used in this example is petrelintide [19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNT-Hyp-NH₂ (SEQ ID NO: 2) as described elsewhere herein.

30 The GIPR / GLP-1R dual agonist used in this example is tirzepatide Hy-Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]AFVQWLIAGGPSSGAPPPS-NH₂ (SEQ ID NO: 4) as described elsewhere herein.

Healthy male Sprague Dawley rats were obtained from Charles River (Germany). The rats
35 were 6 weeks of age at arrival and were allowed to acclimatize for 2 weeks. To generate DIO rats for the study, animals were fed with a high diet containing 60% of total energy from fat (D12492, Research Diet Inc., New Brunswick, USA) ad libitum for 18 weeks. Animals

were housed in groups of 2, on a 12-hour light and 12-hour dark cycle (with lights on at 10.00 PM-10:00 AM) at standard temperature and humidity conditions (20-23°C, 50-80% relative humidity) with ad libitum access to domestic quality tap water.

- 5 DIO animals (n=12/group) were stratified based on bodyweight on day -12. Beginning with day 0, rats were treated once daily for 13 days either with vehicle (group 1 and group 2) or tirzepatide at 10 nmol/kg (group 3 and group 4) by subcutaneous injection.

On day 14 and until day 34, rats dosed with vehicle continued vehicle treatment. Every
10 second day (Q2D), group 1 received a second injection of vehicle and group 2 received an injection of amylin analogue at 10 nmol/kg every second day on top of vehicle. At the same time, rats dosed with tirzepatide continued tirzepatide treatment and additionally received either an injection of vehicle (group 3) or amylin analogue 10 nmol/kg (group 4) every
15 second day.

The study design is depicted diagrammatically in **Figure 1**.

Food intake and water intake were measured every day from day -4 and throughout the experiment, and the cumulative food intake and cumulative water intake for each treatment
20 group was calculated (**Figure 2** and **Figure 3**).

On day 34 blood samples were drawn to determine the plasma exposure concentration of both amylin analogue and tirzepatide. Blood samples were drawn prior to the final dose of both compounds, then 6 h and 24 h post-dose. At each sampling time point, samples from
25 the rats were drawn by tail cut and processed to plasma by centrifugation for 5 minutes at 8,300 x g at 4°C.

Plasma samples were analyzed after solid phase extraction (SPE) by liquid chromatography mass spectrometry (LC-MS/MS). The bioanalytical assay range was between 1 and 1000
30 nmol/L, and for acceptance at least 75% of the calibration samples and at least 4 of 6 QC samples showed accuracy within $\pm 15\%$, except at LLOQ $\pm 20\%$. At least one QC sample at each level (high, medium, low) was accepted for a valid assay result. A summary of the measured exposure is summarized in T 1.

35 **Table 1 – Measured exposure of amylin analogue and Tirzepatide**

		amylin analogue	Tirzepatide
--	--	-----------------	-------------

	Time (h)	Mean (nmol/L)	SD (nmol/L)	Coefficient of variation (%)	Mean (nmol/L)	SD (nmol/L)	Coefficient of variation (%)
amylin analogue 10 nmol/kg (Q2D)	0	103	10.0	9.7	N/A	N/A	N/A
	6	77.8	9.7	12.5	N/A	N/A	N/A
	24	96.9	9.0	9.3	N/A	N/A	N/A
Tirzepatide 10 nmol/kg (QD)	0	N/A	N/A	N/A	35.0	5.5	15.7
	6	N/A	N/A	N/A	36.4	8.0	22.0
	24	N/A	N/A	N/A	44.6	12.6	28.2
amylin analogue 10 nmol/kg (Q2D) and Tirzepatide 10 nmol/kg (QD)	0	115	9.7	8.4	41.7	6.2	14.8
	6	76.8	11.6	15.1	31.2	9.0	28.7
	24	98.2	8.7	8.9	42.8	6.7	15.7

Animals were weighed on day -4 and every day throughout the study. The percent (%) body weight change from baseline was calculated for each day from day 0 to 34 (**Figure 4**). It can be seen in Figure 4 that upon treatment with tirzepatide, body weight is initially reduced, but then plateaus (i.e., ceases to be further reduced, staying at the same body weight) from about day 11. However, combined treatment with tirzepatide and petrelintide (starting at day 14) causes a further reduction in body weight, in contrast to continued treatment with solely tirzepatide (for which body weight remains essentially the same for the rest of the study period). Thus, additional treatment with petrelintide may be a useful option for further weight reduction particularly for subjects taking tirzepatide, but in which body weight has plateaued.

The mean weight change at day 34 is also shown in **Figure 10**.

Combined treatment with the amylin analogue and tirzepatide achieved a significant, sustained and greater cumulative food intake inhibition and a corresponding significant, sustained and greater body weight reduction compared to vehicle- and each mono-treated group ($-5.2\% \pm 0.7$ amylin analogue, $-8.2\% \pm 1.1$ tirzepatide, $-15.3\% \pm 0.9$ combination, $6.5\% \pm 0.4$, vehicle; relative to initial body weights $\pm$ SEM).

Exposure of amylin analogue and tirzepatide was determined on the last day (day 34) of the experiment at three different time-points. The exposure measured was similar for each compound between comparative groups (**Figures 6-9**).

In conclusion, in DIO rats the combined treatment with the amylin analogue and tirzepatide showed significantly greater body weight loss compared to treatment with either peptide alone, clearly indicating the potential use of this combination therapy for the management of overweight, obesity and obesity-related comorbidities.

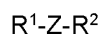
5

All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described methods and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred

10 embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in biochemistry, molecular biology or related fields are intended to be within the scope of the following aspects.

CLAIMS

1. An amylin analogue and a gastric inhibitory polypeptide receptor (GIPR) / glucagon-like peptide-1 receptor (GLP-1R) dual agonist for use in treating or preventing a disease in a
 5 subject, wherein the amylin analogue is a compound of the formula:



wherein:

R¹ is hydrogen, C₁₋₄ acyl, benzoyl or C₁₋₄ alkyl, or a half-life extending moiety M, wherein M is optionally linked to Z via a linker moiety L;

- 10 R² is OH or NHR³, wherein R³ is hydrogen or C₁₋₃-alkyl; and

Z is an amino acid sequence of formula I:

X1-X2-X3-X4-X5-X6-X7-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-
 Phe-Gly(Me)-Ala-Ile(Me)-X27-Ser-Ser-Thr-Glu-X32-Gly-Ser-X35-Thr-X37 (SEQ ID
 NO: 1)

- 15 wherein:

X1 is selected from the group consisting of Arg, Lys and Glu;

X2 and X7 are amino acid residues whose side chains together form a lactam bridge;

X3 is selected from the group consisting of Gly, Gln and Pro;

X4 is selected from the group consisting of Thr and Glu;

- 20 X5 is selected from the group consisting of Ala and Leu;

X6 is selected from the group consisting of Thr and Ser;

X10 is selected from the group consisting of Glu and Gln;

X14 is selected from the group consisting of Aad, His, Asp, Asn and Arg;

X17 is selected from the group consisting of Gln, His and Thr;

- 25 X19-X20 is selected from Ser-Ser, Thr-Thr, Ala-Thr, Ala-Ala, Gly-Thr, Gly-Gly and
 Ala-Asn or is absent;

X27 is selected from the group consisting of Leu and Pro;

X32 is selected from the group consisting of Val and Thr;

X35 is selected from the group consisting of Asn and Ser;

- 30 X37 is selected from the group consisting of Hyp and Pro; and

Hyp is 4-hydroxyproline,

Gly(Me) is N-methylglycine [also known as sarcosine (Sar)],

Ile(Me) is N-methylisoleucine, and

- 35 Aad is 2-aminoadipic acid, e.g. (2S)-2-aminoadipic acid [also (2S)-2-
 aminohexanedioic acid], also known as homo-glutamic acid;

or a pharmaceutically acceptable salt or solvate thereof, and

wherein the disease is overweight, obesity, morbid obesity, diabetes, or a disease linked to obesity or to diabetes.

2. The amylin analogue and GIPR / GLP-1R dual agonist for use according to claim 1,
 5 wherein the disease linked to obesity or to diabetes is selected from the group consisting of:
 obesity-linked inflammation, obesity-linked gallbladder disease, obesity-induced sleep
 apnea, obesity-linked respiratory problems, degeneration of cartilage, osteoarthritis,
 infertility, Alzheimer's disease, pre-diabetes, gestational diabetes, insulin resistance
 10 syndrome, inadequate glucose control, impaired glucose tolerance (IGT), disease states
 associated with elevated blood glucose levels, metabolic disease, metabolic syndrome,
 hyperglycemia, hypertension, dyslipidaemia, atherogenic dyslipidemia, kidney failure,
 arteriosclerosis, atherosclerosis, macrovascular disease, microvascular disease, diabetic
 heart disease, diabetic cardiomyopathy, heart failure as a diabetic complication, coronary
 heart disease, peripheral artery disease and stroke.

15

3. An amylin analogue and a GIPR / GLP-1R dual agonist for use in a method of
 inhibiting weight gain and/or reducing body weight in a subject, wherein the amylin analogue
 is a compound of the formula:



20 wherein:

R^1 is hydrogen, C_{1-4} acyl, benzoyl or C_{1-4} alkyl, or a half-life extending moiety M, wherein M
 is optionally linked to Z via a linker moiety L;

R^2 is OH or NHR^3 , wherein R^3 is hydrogen or C_{1-3} -alkyl; and

Z is an amino acid sequence of formula I:

25 X1-X2-X3-X4-X5-X6-X7-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-
 Phe-Gly(Me)-Ala-Ile(Me)-X27-Ser-Ser-Thr-Glu-X32-Gly-Ser-X35-Thr-X37 (SEQ ID
 NO: 1)

wherein:

30 X1 is selected from the group consisting of Arg, Lys and Glu;
 X2 and X7 are amino acid residues whose side chains together form a lactam bridge;
 X3 is selected from the group consisting of Gly, Gln and Pro;
 X4 is selected from the group consisting of Thr and Glu;
 X5 is selected from the group consisting of Ala and Leu;
 X6 is selected from the group consisting of Thr and Ser;
 35 X10 is selected from the group consisting of Glu and Gln;
 X14 is selected from the group consisting of Aad, His, Asp, Asn and Arg;
 X17 is selected from the group consisting of Gln, His and Thr;

- X19-X20 is selected from Ser-Ser, Thr-Thr, Ala-Thr, Ala-Ala, Gly-Thr, Gly-Gly and Ala-Asn or is absent;
 X27 is selected from the group consisting of Leu and Pro;
 X32 is selected from the group consisting of Val and Thr;
 5 X35 is selected from the group consisting of Asn and Ser;
 X37 is selected from the group consisting of Hyp and Pro; and
 Hyp is 4-hydroxyproline,
 Gly(Me) is N-methylglycine [also known as sarcosine (Sar)],
 Ile(Me) is N-methylisoleucine, and
 10 Aad is 2-aminoadipic acid, e.g. (2S)-2-aminoadipic acid [also (2S)-2-aminohexanedioic acid], also known as homo-glutamic acid;
 or a pharmaceutically acceptable salt or solvate thereof.

4. A non-therapeutic method of inhibiting weight gain and/or reducing body weight in a
 15 subject, wherein the method comprises administering an amylin analogue and a GIPR / GLP-1R dual agonist to the subject, wherein the amylin analogue is a compound of the formula:



wherein:

- 20 R^1 is hydrogen, C_{1-4} acyl, benzoyl or C_{1-4} alkyl, or a half-life extending moiety M, wherein M is optionally linked to Z via a linker moiety L;
 R^2 is OH or NHR^3 , wherein R^3 is hydrogen or C_{1-3} -alkyl; and
 Z is an amino acid sequence of formula I:

- 25 X1-X2-X3-X4-X5-X6-X7-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-X27-Ser-Ser-Thr-Glu-X32-Gly-Ser-X35-Thr-X37 (SEQ ID NO: 1)

wherein:

- X1 is selected from the group consisting of Arg, Lys and Glu;
 X2 and X7 are amino acid residues whose side chains together form a lactam bridge;
 30 X3 is selected from the group consisting of Gly, Gln and Pro;
 X4 is selected from the group consisting of Thr and Glu;
 X5 is selected from the group consisting of Ala and Leu;
 X6 is selected from the group consisting of Thr and Ser;
 X10 is selected from the group consisting of Glu and Gln;
 35 X14 is selected from the group consisting of Aad, His, Asp, Asn and Arg;
 X17 is selected from the group consisting of Gln, His and Thr;

X19-X20 is selected from Ser-Ser, Thr-Thr, Ala-Thr, Ala-Ala, Gly-Thr, Gly-Gly and Ala-Asn or is absent;
 X27 is selected from the group consisting of Leu and Pro;
 X32 is selected from the group consisting of Val and Thr;
 5 X35 is selected from the group consisting of Asn and Ser;
 X37 is selected from the group consisting of Hyp and Pro; and
 Hyp is 4-hydroxyproline,
 Gly(Me) is N-methylglycine [also known as sarcosine (Sar)],
 Ile(Me) is N-methylisoleucine, and
 10 Aad is 2-aminoadipic acid, e.g. (2S)-2-aminoadipic acid [also (2S)-2-aminohexanedioic acid], also known as homo-glutamic acid;
 or a pharmaceutically acceptable salt or solvate thereof.

5. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one
 15 of claims 1 to 3 or the method according to claim 4, wherein the amylin analogue comprises the amino acid sequence
 RDGTATKATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTNT-Hyp (SEQ ID NO: 9)
 or a variant thereof having at least 80% identity to SEQ ID NO: 9, preferably at least 85%
 identity, at least 86% identity, at least 87% identity, at least 88% identity, at least 89%
 20 identity, at least 90% identity, at least 91% identity, at least 92% identity, at least 93%
 identity, at least 94% identity, at least 95% identity, at least 96%, at least 97%, at least 98%
 or at least 99% identity to SEQ ID NO: 9.

6. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one
 25 of claims 1 to 3 or 5, or the method according to claim 4 or claim 5, wherein the amylin analogue is petrelintide:
 [19CD]-isoGlu-RD()₂GTATK()₂ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-
 LSSTEVGSTNT-Hyp-NH₂ (SEQ ID NO: 2),
 wherein () after amino acid symbols indicate residues whose side chains participate
 30 in an intramolecular lactam bridge, and
 [19CD]-isoGlu is a 19-carboxynonadecanoyl group ([19-CD]-) covalently attached to
 the alpha amino group of an iso-glutamic acid linker,
 or a pharmaceutically acceptable salt or solvate thereof.

35 7. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one
 of claims 1 to 3, 5 or 6, or the method according to any one of claims 4 to 6, wherein the
 amylin analogue is administered to the subject at a dose of up to about 10 mg, preferably a

dose selected from any one of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg and about 10 mg.

8. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 7, or the method according to any one of claims 4 to 7, wherein the amylin analogue is administered to the subject once a week.

9. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 8, or the method according to any one of claims 4 to 8, wherein the GIPR / GLP-1R dual agonist comprises the amino acid sequence Y[Aib]EGTFTSDYSI[Aib]LDKIAQKAFVQWLIAGGPSSGAPPPS (SEQ ID NO: 10) or a variant thereof having at least 80% identity to SEQ ID NO: 10, preferably at least 85% identity, at least 86% identity, at least 87% identity, at least 88% identity, at least 89% identity, at least 90% identity, at least 91% identity, at least 92% identity, at least 93% identity, at least 94% identity, at least 95% identity, at least 96%, at least 97%, at least 98% or at least 99% identity to SEQ ID NO: 10.

10. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 9, or the method according to any one of claims 4 to 9, wherein the GIPR / GLP-1R dual agonist is of the formula:

Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]A-X-VQWLIAGGPSSGAPPPS (SEQ ID NO: 3)
wherein:

[Aib] is α -aminoisobutyric acid,

[K] is lysine with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)_a-CO-(CH₂)_b-CO₂H conjugated to the epsilon-amino group of the lysine side-chain,

a is 1 or 2, b is 10 to 20, X is Phe or 1-Nal, and the C-terminal amino acid is optionally amidated as a C-terminal primary amide;

or a pharmaceutically acceptable salt or solvate thereof.

11. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 10, or the method according to any one of claims 4 to 10, wherein the GIPR / GLP-1R dual agonist is tirzepatide:

Hy-Y[Aib]EGTFTSDYSI[Aib]LDKIAQ[K]AFVQWLIAGGPSSGAPPPS-NH₂ (SEQ ID NO: 4)

wherein

[Aib] is α -aminoisobutyric acid, and

[K] is lysine with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(isoGlu)₁-CO-(CH₂)₁₈-COOH conjugated to the epsilon-amino group of the lysine side-chain; or a pharmaceutically acceptable salt or solvate thereof.

5 12. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 11, or the method according to any one of claims 4 to 11, wherein the amylin analogue is petrelintide and the GIPR / GLP-1R dual agonist is tirzepatide.

10 13. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 12, or the method according to any one of claims 4 to 12, wherein the GIPR / GLP-1R dual agonist is administered to the subject at a dose of up to about 15 mg, preferably a dose selected from any one of about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg and about 15 mg.

15 14. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 13, or the method according to any one of claims 4 to 13, wherein the GIPR / GLP-1R dual agonist is administered to the subject once a week.

20 15. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 14, or the method according to any one of claims 4 to 14, wherein the amylin analogue, or the pharmaceutically acceptable salt or solvate thereof, is formulated as an amylin analogue pharmaceutical composition.

25 16. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 15, or the method according to any one of claims 4 to 15, wherein the GIPR / GLP-1R dual agonist, or the pharmaceutically acceptable salt or solvate thereof, is formulated as a GIPR / GLP-1R dual agonist pharmaceutical composition.

30 17. The amylin analogue and GIPR / GLP-1R dual agonist for use according to any one of claims 1 to 3 or 5 to 16, or the method according to any one of claims 4 to 16, wherein the amylin analogue and GIPR / GLP-1R dual agonist are administered to the subject by injection, preferably by subcutaneous injection.

35 18. A kit comprising an amylin analogue and a GIPR / GLP-1R dual agonist, preferably wherein the amylin analogue and/or the GIPR / GLP-1R dual agonist are as defined in any one of claims 1 to 17.