

COMBINATION THERAPY

FIELD OF THE INVENTION

The present invention relates to therapeutic methods using a combination of an acylated compound having dual agonist activity at the GLP-1 (glucagon-like-peptide 1) and GLP-2 (glucagon-like peptide 2) receptors and a peptide hormone. In particular, the invention relates to the combination of a dual GLP-1/GLP-2 agonist peptide, and an amylin analogue, for the regulation of body weight and for the prophylaxis or treatment of 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 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.

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 is evidence to suggest that the effect of GLP-1 may be impaired in obese subjects, suggesting that GLP-1 agonists may have promise the in treatment of obesity.

Intestinal tissue is responsible for the production of both human glucagon-like peptide 1 (GLP-1(7-36)) and human glucagon-like peptide 2 (GLP-2 (1-33)), which are produced by the same cells. Human GLP-2 is a 33-amino-acid peptide with the sequence:

Hy-His-Ala-Asp-Gly-Ser-Phe-Ser-Asp-Glu-Met-Asn-Thr-Ile-Leu-Asp-Asn-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Asn-Trp-Leu-Ile-Gln-Thr-Lys-Ile-Thr-Asp-OH
(SEQ ID NO: 1).

GLP-2 is derived from specific posttranslational processing of proglucagon in the enteroendocrine L cells of the intestine and in specific regions of the brainstem. GLP-2 binds to a single G-protein-coupled receptor belonging to the class II glucagon secretin family.

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GLP-2 is co-secreted with GLP-1, oxyntomodulin and glicentin, in response to nutrient ingestion. Human GLP-1 is produced as a 30-amino acid peptide with the sequence:

Hy-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-
10 Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly-NH₂
(SEQ ID NO: 2).

GLP-1 has been described as a physiological incretin hormone and has thus been mostly reported to augment an insulin response after an oral intake of glucose or fat.
15 It is, however, generally understood that GLP-1 lowers glucagon concentrations, has beneficial effects on inhibition of fast bowel movements (Tolessa et al., 1998, Dig. Dis. Sci. 43(10): 2284-90), and slows gastric emptying.

A major drawback of GLP-1 therapy is that a significant proportion of patients taking
20 known GLP-1 agonists suffer from side effects of nausea and vomiting (Filippatos et al, 2014/15, Rev Diabet Stud., 11(3): 202-230). These side-effects generally require the dose of the GLP-1 agonist to be gradually escalated from a low starting dose in order to minimize such side effects. Indeed, clinical trial data for the GLP-1 agonist Semaglutide shows that nausea and vomiting were commonly observed in patients
25 when administered even when initially administering low doses of the drug (Wilding et al, 2021, N Engl J Med; 384:989-1002). These side-effects are undesirable in that they are liable to reduce patient compliance with treatment.

There is therefore an ongoing need for therapeutics with GLP-1 agonist activity that
30 are effective in the treatment of obesity and related conditions while not exhibiting the expected side effects of nausea and vomiting upon administration.

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

WO 2018/104561 discloses peptides having dual GLP-1 and GLP-2 agonist activity and proposes medical uses thereof and PCT/EP2022/074420 specific dosage regimes for the treatment of obesity and related conditions.

- 5 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 islets of pancreases from type 2 diabetes
10 patients.

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

15 H-KC()^{NTATC()}ATQRLANFLVHSSN^{NFGAILSSTNVGSNTY}-NH₂
(SEQ ID NO: 3)

- wherein H- 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 -
20 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 and 7 indicate the presence of an intramolecular disulfide bridge between the two Cys residues in question.

- 25 Amylin may be beneficial in treating metabolic disorders such as diabetes and/or obesity. Amylin is believed to regulate gastric emptying, and to suppress glucagon secretion and 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 have no circulating amylin, and type 2 diabetes
30 patients exhibit reduced postprandial amylin concentrations. WO 93/10146 describes an amylin analogue known as pramlintide, which has the sequence:

35 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 NO: 4).

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.

- 5 An alternative amylin analogue incorporating N-methylated residues and having a reduced 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.

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WO 2018/046719 describes amylin analogues having, inter alia, a lactam bridge instead of a 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).

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SUMMARY OF THE INVENTION

Broadly, the present invention relates to therapies and methods for the prevention or treatment of diseases and disorders, such as obesity and obesity-related conditions.

- 20 More specifically, the invention is based on the surprising finding that the combination of the use of a GLP-1 (glucagon-like peptide 1) and GLP-2 (glucagon-like peptide 2) receptor dual agonist, and a long-acting amylin analogue results in greater treatment efficacy as compared with treatment of either agent alone.

- 25 In one aspect, there is provided a GLP-1/GLP-2 dual agonist and an amylin analogue for use in a method of preventing or treating a disease or disorder, wherein the GLP-1/GLP-2 dual agonist and the amylin analogue are administered to a subject.

In one embodiment, the subject is a human subject.

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In one embodiment, the subject is a human subject suffering from a disease or disorder.

In one embodiment, the subject is a human subject at risk of developing a disease or disorder.

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In one embodiment, the dose of the GLP-1/GLP-2 dual agonist and dose of the amylin analogue are independently selected.

5 In one embodiment, the GLP-1/GLP-2 dual agonist may be administered at a dose of 100 nmol/kg and the amylin analogue may be administered at a dose of 10 nmol/kg.

10 In one embodiment, the disease or disorder is obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia, diabetes, pre-diabetes, metabolic syndrome or hypertension.

15 The invention further relates to the administration of a GLP-1/GLP-2 dual agonist and an amylin analogue for use in methods that are not directed towards treating diseases or disorders, *per se*. Such uses and methods may be considered preventative of diseases or disorders in so far as they may be utilised prior to the onset of disease (e.g., pre diagnosis) e.g., to ameliorate unwanted physiological characteristics or alter certain physiological parameters.

20 In some embodiments the uses or methods of the invention may be considered considered cosmetic.

In one embodiment, the subject to which the GLP-1/GLP-2 dual agonist and amylin analogue are administered is not suffering from a disease or disorder.

25 In one aspect, there is provided the combination of a GLP-1/GLP-2 dual agonist and an amylin analogue for use for use in a method of reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss, wherein the GLP-1/GLP-2 dual agonist and the amylin analogue are administered.

30 The present invention further provides the combination of a GLP-1/GLP-2 dual agonist and amylin analogue for use in therapy. In yet another aspect there is provided the combination of a GLP-1/GLP-2 dual agonist and amylin analogue for use as a medicament. Also provided is a combination of a GLP-1/GLP-2 dual agonist and
35 amylin analogue for use in a method of medical treatment.

The invention also provides a combination of a GLP-1/GLP-2 dual agonist and an amylin analogue for use in a method of reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss.

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The invention also provides a combination of a GLP-1/GLP-2 dual agonist and an amylin analogue for use in a method of prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio), diabetes (e.g. Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome or hypertension.

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The invention also provides a method of reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss in a subject in need thereof, the method comprising administering a GLP-1/GLP-2 dual agonist and an amylin analogue to the subject.

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The invention also provides a method of prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio), diabetes (e.g. Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome or hypertension in a subject in need thereof, the method comprising administering a GLP-1/GLP-2 dual agonist and amylin analogue to the subject.

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The invention also provides a GLP-1/GLP-2 dual agonist and an amylin analogue for use in the preparation of one or more medicaments for the administration of the GLP-1/GLP-2 dual agonist and the amylin analogue. In this respect, the GLP-1/GLP-2 dual agonist and the amylin analogue may be in the same or different medicament. In preferred aspect, the GLP-1/GLP-2 dual agonist and the amylin analogue are in separate medicament. In a preferred aspect, the GLP-1/GLP-2 dual agonist is in one medicament that optionally comprises one or more carrier(s), diluent(s) and excipient(s) (sometimes referred to as "GLP-1/GLP-2 dual agonist medicament" or "dual agonist medicament" or "GLP-1/GLP-2 dual agonist pharmaceutical" or "dual agonist pharmaceutical") and wherein the amylin analogue is in another medicament that optionally comprises one or more carrier(s), diluent(s), excipient(s) (sometimes

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- referred to as "amylin analogue medicament" or "amylin analogue pharmaceutical").
The GLP-1/GLP-2 dual agonist medicament may be in any form for suitable administration to a subject. In a preferred aspect, the GLP-1/GLP-2 dual agonist medicament is in a form for suitable subcutaneous (s/c or s.c.) administration to a subject.
- 5 The amylin analogue medicament may be in any form for suitable administration to a subject. In a preferred aspect, the amylin analogue medicament is in a form for suitable subcutaneous (s/c or s.c.) administration to a subject. The GLP-1/GLP-2 dual agonist medicament and the amylin analogue medicament may be delivered to the subject at the same time or at a different time. In a preferred aspect,
- 10 the GLP-1/GLP-2 dual agonist medicament is delivered to the subject daily. In a preferred aspect, the GLP-1/GLP-2 dual agonist medicament is delivered to the subject once daily. In a preferred aspect, the amylin analogue medicament is delivered to the subject every other day. In a preferred aspect, the amylin analogue medicament is delivered to the subject once every other day.
- 15 For some embodiments, preferably the method comprises administering the GLP-1/GLP-2 dual agonist to the subject at a dose of about 0.5 mg to about 10.0 mg.
- For some embodiments, preferably the method comprises administering the GLP-1/GLP-2 dual agonist to the subject at a dose of about 0.5 mg to about 7.5 mg,
- 20 preferably about 1.0 mg to about 7.5 mg, preferably about 1.0 to about 6.0 mg, preferably about 1.0 to about 4.0 mg, preferably about 1.0 to about 3.5 mg.
- For some embodiments, preferably the method comprises administering the GLP-1/GLP-2 dual agonist to the subject once a day at a dose of about 0.5 mg to about 10.0 mg per day.
- 25 For some embodiments, preferably the method comprises administering the GLP-1/GLP-2 dual agonist to the subject once a day at a dose of about 0.5 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 to about 6.0 mg per day, preferably once a day at a dose of about 1.0 to about 4.0 mg per day, preferably once a day at a dose of about 1.0 to about 3.5 mg per day.
- 30 For some embodiments, preferably the GLP-1/GLP-2 dual agonist is in a pharmaceutical composition, wherein the pharmaceutical composition comprises one or more of:
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- (i) at least about 1 mg/mL of one or more GLP-1/GLP-2 dual agonist
- (ii) 5 mM to about 50 mM of phosphate buffer component
- (iii) about 190 mM to about 240 mM of mannitol and/or
- (iv) the pH is about pH 8.0.

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For some embodiments, preferably the method comprises administering the amylin analogue to the subject at a dose of about 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,

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preferably about 2.4 to about 4.0 mg, preferably about 2.4 to about 3.5 mg.

For some embodiments, preferably the method comprises administering the amylin analogue to the subject every other day at a dose of about 0.5 mg to about 10.0 mg per day, preferably every other day at a dose of about 0.6 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 4.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 3.5 mg mg per day.

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For some embodiments, preferably the amylin analogue is in a pharmaceutical composition, wherein the pharmaceutical composition comprises one or more of:

(i) at a concentration of from about 0.4 mg/ml to about 25 mg/ml of one or more amylin analogue;

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(ii) present in a solution with a buffer concentration of about 0.5 mM to 25 mM;

(iii) present in a solution with a pH of about 5.8 to about 6.9; and/or

(iv) provided as a chloride salt.

For some embodiments, preferably the method comprises administering the GLP-1/GLP-2 dual agonist to the subject once a day at a dose of about 0.5 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 to about 6.0 mg per day, preferably once a day at a dose of about 1.0 to about 4.0 mg per day, preferably once a day at a dose of about 1.0 to about 3.5 mg per day;

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and wherein the method comprises administering the amylin analogue to the subject every other day at a dose of about 0.5 mg to about 10.0 mg per day, preferably every other day at a dose of about 0.6 mg to about 7.5 mg mg per day, preferably every

other day at a dose of about 1.2 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 4.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 3.5 mg mg per day.

For some embodiments, preferably the method comprises administering the GLP-1/GLP-2 dual agonist to the subject once a day at a dose of about 0.5 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 to about 6.0 mg per day, preferably once a day at a dose of about 1.0 to about 4.0 mg per day, preferably once a day at a dose of about 1.0 to about 3.5 mg per day;

wherein the GLP-1/GLP-2 dual agonist is in a first pharmaceutical composition, wherein the first pharmaceutical composition comprises one or more of:

- (i) at least about 1 mg/mL of one or more GLP-1/GLP-2 dual agonist
- (ii) 5 mM to about 50 mM of phosphate buffer component
- (iii) about 190 mM to about 240 mM of mannitol and/or
- (iv) the pH is about pH 8.0;

wherein the method comprises administering the amylin analogue to the subject every other day at a dose of about 0.5 mg to about 10.0 mg per day, preferably every other day at a dose of about 0.6 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 4.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 3.5 mg mg per day; and

wherein the amylin analogue is in a second pharmaceutical composition, wherein the second pharmaceutical composition comprises one or more of:

- (i) at a concentration of from about 0.4 mg/ml to about 25 mg/ml of one or more amylin analogue;
- (ii) present in a solution with a buffer concentration of about 0.5 mM to 25 mM;
- (iii) present in a solution with a pH of about 5.8 to about 6.9; and/or
- (iv) the amylin analogue is provided as a chloride salt.

For some embodiments, preferably the method comprises administering the GLP-1/GLP-2 dual agonist to the subject once a day at a dose of about 0.5 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 mg to about 7.5 mg per day,

preferably once a day at a dose of about 1.0 to about 6.0 mg per day, preferably once a day at a dose of about 1.0 to about 4.0 mg per day, preferably once a day at a dose of about 1.0 to about 3.5 mg per day;

wherein the GLP-1/GLP-2 dual agonist is in a first pharmaceutical composition,

5 wherein the first pharmaceutical composition comprises:

- (i) at least about 1 mg/mL of one or more GLP-1/GLP-2 dual agonist
- (ii) 5 mM to about 50 mM of phosphate buffer component
- (iii) about 190 mM to about 240 mM of mannitol and/or
- (iv) the pH is about pH 8.0;

10 wherein the method comprises administering the amylin analogue to the subject every other day at a dose of about 0.5 mg to about 10.0 mg per day, preferably every other day at a dose of about 0.6 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 to about 6.0 mg mg per day, preferably every other day at a dose of
15 about 2.4 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 4.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 3.5 mg mg per day; and

wherein the amylin analogue is in a second pharmaceutical composition, wherein the second pharmaceutical composition comprises:

- 20 (i) at a concentration of from about 0.4 mg/ml to about 25 mg/ml of one or more amylin analogue;
- (ii) present in a solution with a buffer concentration of about 0.5 mM to 25 mM;
 - (iii) present in a solution with a pH of about 5.8 to about 6.9; and/or
 - (iv) the amylin analogue is provided as a chloride salt.

25 The invention also provides the use of a GLP-1/GLP-2 dual agonist and amylin analogue in the preparation of a medicament for reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss.

30 The invention also provides the use of GLP-1/GLP-2 dual agonist and amylin analogue in the preparation of a medicament for prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia (e.g. elevated LDL
35 levels or reduced HDL/LDL ratio), diabetes (e.g. Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome or hypertension.

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

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

- 5 Compounds that have agonist activity at the GLP-1 (glucagon-like peptide 1) and GLP-2 (glucagon-like peptide 2) receptors, e.g. as assessed in *in vitro* potency assays. Such compounds are referred to in this specification as “GLP-1/GLP-2 dual agonists”, or simply “dual agonists”. Thus, the compounds of the present invention have activities of both GLP-1 and GLP-2.

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In one embodiment, the GLP-1/GLP-2 dual agonist is:

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]
QAARDFIAWLIQHKITD-OH (SEQ ID NO: 5).

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

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

The composition may be a pharmaceutical composition. The pharmaceutical

- 20 composition may be formulated as a liquid suitable for administration by injection or infusion.

In one embodiment, the amylin analogue is:

[19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-

- 25 LSSTEVGSTNT-Hyp-NH₂ (SEQ ID NO: 6).

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

- 30 The invention also provides a composition comprising the amylin analogue of the invention, or a pharmaceutically acceptable salt or solvate thereof, together with a carrier, excipient or vehicle. The carrier may be a pharmaceutically acceptable carrier.

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

5 BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Effect of s.c. treatment with vehicle, the GLP-1/GLP-2 dual agonist, the amylin analogue and combination therapy on cumulative food intake in Sprague Dawley diet-induced obese (DIO) rats. Data are shown as mean values (n= 9/group). Statistics: The cumulated food intake on day 28 (from day 0-28) were compared by one-way ANOVA followed by Bonferroni multiple comparison's test, 95% confidence interval.

Figure 2: Effect of s.c. treatment with vehicle, the GLP-1/GLP-2 dual agonist or the amylin analogue monotherapy and the GLP-1/GLP-2 dual agonist and the amylin analogue combination therapy on % changes in body weight (BW) in Sprague Dawley diet-induced obese (DIO) rats from baseline day 0. Data are shown as mean values (n= 9/group) A) Daily changes in % BW B) Change in BW on day 28. Statistics: Data in B) were compared by one-way ANOVA followed by Bonferroni multiple comparison's test, 95% confidence interval.

Figure 3: Effect of subcutaneous (s.c.) treatment with vehicle, the GLP-1/GLP-2 dual agonist or the amylin analogue monotherapy and the GLP-1/GLP-2 dual agonist and the amylin analogue combination therapy on overnight fasting blood glucose levels in Sprague Dawley diet-induced obese (DIO) rats at day 29. Data are shown as mean values (n= 9/group). Dotted line shows the average fasting blood glucose levels at baseline from all animals in the study. Statistics: Data in were compared by one-way ANOVA followed by Bonferroni multiple comparison's test, 95% confidence interval.

Figure 4: Plasma exposure in nmol/L, measured using LC-MS/MS for:

- A. GLP-1/GLP-2 dual agonist dosed 100 nmol/kg either individually or in combination with amylin analogue 10 nmol/kg.
- B. Amylin analogue dosed 10 nmol/kg either individually or in combination with GLP-1/GLP-2 dual agonist 100 nmol/kg. Data are shown as mean values (n= 9/group) with error bars representing one standard deviation.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of,
5 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.

10 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.

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

15 Definitions

Unless specified otherwise, the following definitions are provided for specific terms which are used in the present written description.

20 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.

25 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.

30 The terms “patient”, “subject” and “individual” may be used interchangeably 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).

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
5 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.

The term “agonist” as employed in the context of the invention refers to a substance
10 (ligand) that activates the receptor type in question.

Throughout the present description and claims 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
15 (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 sarcosine (Sar), norleucine (Nle), α -aminoisobutyric acid (Aib), 2,3-diaminopropanoic acid (Dap), 2,4-diaminobutanoic acid (Dab) and 2,5-diaminopentanoic acid (ornithine;
20 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
25 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-” moiety at the amino terminus (N-terminus) of the sequence, and either an “-OH” moiety or an “-
30 NH₂” moiety at the carboxy terminus (C-terminus) of the sequence. In such cases, and unless otherwise indicated, a “Hy-” 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], while an “-OH” or an “-NH₂” moiety at the C-terminus of the sequence
35 indicates a hydroxy group [e.g. R² = OH in general formulas; corresponding to the presence of a carboxy (COOH) group at the C-terminus] or an amino group [e.g. R² =

[NH₂] in the general formulas; corresponding to the presence of an amido (CONH₂) group at the C-terminus], respectively. In each sequence of the invention, a C-terminal “-OH” moiety may be substituted for a C-terminal “-NH₂” moiety, and vice-versa.

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“Percent (%) amino acid sequence identity” with respect to the GLP-2 polypeptide sequences 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.

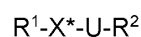
Dual agonist compounds

Compounds that have agonist activity at the GLP-1 (glucagon-like peptide 1) and GLP-2 (glucagon-like peptide 2) receptors, e.g. as assessed in *in vitro* potency assays. Such compounds are referred to herein as “GLP-1/GLP-2 dual agonists”, or “dual agonists”. Thus, the compounds of the present invention have activities of both GLP-1 and GLP-2.

Dual agonist compounds according to the present invention have activities of both GLP-1 (7-36) and GLP-2 (1-33).

A GLP-1/GLP-2 dual agonist of the present invention may be represented by the formula:

35



wherein:

- R¹ is hydrogen (Hy), C₁₋₄ alkyl (e.g. methyl), acetyl, formyl, benzoyl or trifluoroacetyl;
- R² is NH₂ or OH;
- 5 • X* is a peptide of formula I:
H-X2-EG-X5-F-X7-X8-E-X10-X11-TIL-X15-X16-X17-A-X19-X20-X21-FI-X24-WL-X27-X28-X29-KIT-X33 (I) (SEQ ID NO: 7)

wherein:

- 10 ○ X2 is Aib or G
- X5 is T or S;
- X7 is T or S;
- X8 is S, E or D;
- X10 is L, M, V or Ψ;
- X11 is A, N or S;
- 15 ○ X15 is D or E;
- X16 is G, E, A or Ψ;
- X17 is Q, E, K, L or Ψ;
- X19 is A, V or S;
- X20 is R, K or Ψ;
- 20 ○ X21 is D, L or E;
- X24 is A, N or S;
- X27 is I, Q, K, H or Y;
- X28 is Q, E, A, H, Y, L, K, R or S;
- X29 is H, Y, K or Q;
- 25 ○ X33 is D or E;
- U is absent or a sequence of 1-15 residues each independently selected from K, k, E, A, T, I, L and Ψ;
- the molecule contains one and only one Ψ, wherein Ψ is a residue of K, k, R, Orn, Dap or Dab in which the side chain is conjugated to a substituent having the formula Z¹- or Z¹-Z²-, wherein:
- 30 ○ Z¹- is CH₃-(CH₂)₁₀₋₂₂-(CO)- or HOOC-(CH₂)₁₀₋₂₂-(CO)-; and
- -Z²- is selected from -Z^{S1}-, -Z^{S1}-Z^{S2}-, -Z^{S2}-Z^{S1}-, -Z^{S2}-, -Z^{S3}-, -Z^{S1}Z^{S3}-, -Z^{S2}Z^{S3}-, -Z^{S3}Z^{S1}-, -Z^{S3}Z^{S2}-, -Z^{S1}Z^{S2}Z^{S3}-, -Z^{S1}Z^{S3}Z^{S2}-, -Z^{S2}Z^{S1}Z^{S3}-, -Z^{S2}Z^{S3}Z^{S1}-, -Z^{S3}Z^{S1}Z^{S2}-, -Z^{S3}Z^{S2}Z^{S1}-, -Z^{S2}Z^{S3}Z^{S2}- wherein
- 35 ○ Z^{S1} is isoGlu, β-Ala, isoLys, or 4-aminobutanoyl;
- Z^{S2} is -(Peg3)_m- where m is 1, 2, or 3; and

- -Z^{S3}- is a peptide sequence of 1-6 amino acid units independently selected from the group consisting of A, L, S, T, Y, Q, D, E, K, k, R, H, F and G;
- and wherein at least one of X5 and X7 is T;

5

or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the GLP-1/GLP-2 dual agonist is:

Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]
QAARDFIAWLIQHKITD-OH (SEQ ID NO: 5).

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

The invention also provides a composition comprising a dual agonist of the invention, or a pharmaceutically acceptable salt or solvate thereof, together with a carrier,

- 15 excipient or vehicle. The carrier may be a pharmaceutically acceptable carrier.

The composition may be a pharmaceutical composition. The pharmaceutical composition may be formulated as a liquid suitable for administration by injection or infusion.

20 **Dual agonist activity**

In accordance with the present invention, the dual agonist has at least one GLP-1 and at least one GLP-2 biological activity. Exemplary GLP-1 physiological activities include reducing rate of intestinal transit, reducing rate of gastric emptying, reducing appetite, food intake or body weight, and improving glucose control and glucose tolerance. Exemplary GLP-2 physiological activities include causing an increase in

25 intestinal mass (e.g. of small intestine or colon), intestinal repair, and improving intestinal barrier function (i.e. reducing permeability of the intestine). These parameters can be assessed in *in vivo* assays in which the mass and the permeability of the intestine, or a portion thereof, is determined after a test animal has been

30 treated with a dual agonist.

The dual agonists have agonist activity at the GLP-1 and GLP-2 receptors, e.g. the human GLP-1 and GLP-2 receptors. EC₅₀ values for *in vitro* receptor agonist activity may be used as a numerical measure of agonist potency at a given receptor. An EC₅₀

35 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 EC₅₀ at a particular receptor which is lower than the EC₅₀ of a reference compound in the same assay may be considered to have higher potency at that receptor than the reference compound.

5

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 2.0 nM, below 1.5 nM, below 1.0 nM, below 0.9 nM, below 0.8 nM, below 0.7 nM, below 0.6 nM, below 0.5 nM, below 0.4 nM,
10 below 0.3 nM, below 0.2 nM, below 0.1 nM, below 0.09 nM, below 0.08 nM, below 0.07 nM, below 0.06 nM, below 0.05 nM, below 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
15 between 0.005 and 2.5 nM, between 0.01 nM and 2.5 nM, between 0.025 and 2.5 nM, between 0.005 and 2.0 nM, between 0.01 nM and 2.0 nM, between 0.025 and 2.0 nM, between 0.005 and 1.5 nM, between 0.01 nM and 1.5 nM, between 0.025 and 1.5 nM, between 0.005 and 1.0 nM, between 0.01 nM and 1.0 nM, between 0.025 and 1.0 nM, between 0.005 and 0.5 nM, between 0.01 nM and 0.5 nM, between 0.025 and 0.5 nM,
20 between 0.005 and 0.25 nM, between 0.01 nM and 0.25 nM, between 0.025 and 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
25 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:

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

30

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.

35

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 0.001 and 100, e.g. between 0.001 and 10, between 0.001 and 5, between 0.001 and 1, between 0.001 and 0.5, between 0.001 and 0.1, between 0.001 and 0.05, or between 0.001 and 0.01; between 0.01 and 10, between 0.01 and 5, between 0.01 and 1, between 0.01 and 0.5, between 0.01 and 0.1, or between 0.01 and 0.05; between 0.05 and 10, between 0.05 and 5, between 0.05 and 1, between 0.05 and 0.5, or between 0.05 and 0.1; between 0.1 and 10, between 0.1 and 5, between 0.1 and 1, or between 0.1 and 0.5; between 0.5 and 10, between 0.5 and 5, or between 0.5 and 1; between 1 and 10, or between 1 and 5; or between 5 and 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 0.01 and 1, between 0.01 and 0.5 or between 0.01 and 0.1.

By contrast, the dual agonists of the invention have higher potency at the GLP-1 receptor (e.g. the human GLP-1 receptor) than wild type human GLP-2 (hGLP-2 (1-33)) or [Gly2]-hGLP-2 (1-33) (i.e. human GLP-2 having glycine at position 2, also known as teduglutide). Thus, the relative potency of the dual agonists at the GLP-1 receptor compared to hGLP-2 (1-33) or teduglutide is greater than 1, typically greater than 5 or greater than 10, and may be up to 100, up to 500, or even higher.

GLP-2 activity

In some embodiments, the dual agonist has an EC_{50} at the GLP-2 receptor (e.g. the human GLP-2 receptor) which is below 2.0 nM, below 1.5 nM, below 1.0 nM, below 0.9 nM, below 0.8 nM, below 0.7 nM, below 0.6 nM, below 0.5 nM, below 0.4 nM, below 0.3 nM, below 0.2 nM, below 0.1 nM, below 0.09 nM, below 0.08 nM, below 0.07 nM, below 0.06 nM, below 0.05 nM, below 0.04 nM, below 0.03 nM, below 0.02 nM, or below 0.01 nM, e.g. when assessed using the GLP-2 receptor potency assay as described in PCT/EP2022/074420.

In some embodiments, the dual agonist has an EC_{50} at the GLP-2 receptor which is between 0.005 and 2.0 nM, between 0.01 nM and 2.0 nM, between 0.025 and 2.0 nM, between 0.005 and 1.5 nM, between 0.01 nM and 1.5 nM, between 0.025 and 1.5 nM, between 0.005 and 1.0 nM, between 0.01 nM and 1.0 nM, between 0.025 and 1.0 nM, between 0.005 and 0.5 nM, between 0.01 nM and 0.5 nM, between 0.025 and 0.5 nM, between 0.005 and 0.25 nM, between 0.01 nM and 0.25 nM, between 0.025 and 0.25

nM, e.g. when assessed using the GLP-2 receptor potency assay as described in PCT/EP2022/074420.

5 An alternative measure of GLP-2 agonist activity may be derived by comparing the potency of a dual agonist with the potency of a known (or reference) GLP-2 agonist when both are measured in the same assay. Thus the relative potency at the GLP-2 receptor may be defined as:

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

10

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.

15

The reference GLP-2 agonist may, for example, be human GLP-2(1-33) or teduglutide ([Gly2]-hGLP-2 (1-33)), but is preferably teduglutide. Typically the relative potency will be between 0.001 and 100, e.g. between 0.001 and 10, between 0.001 and 5, between 0.001 and 1, between 0.001 and 0.5, between 0.001 and 0.1, between 0.001 and 0.05, or between 0.001 and 0.01; between 0.01 and 10, between 0.01 and 5, between 0.01 and 1, between 0.01 and 0.5, between 0.01 and 0.1, or between 0.01 and 0.05; between 0.05 and 10, between 0.05 and 5, between 0.05 and 1, between 0.05 and 0.5, or between 0.05 and 0.1; between 0.1 and 10, between 0.1 and 5, between 0.1 and 1, or between 0.1 and 0.5; between 0.5 and 10, between 0.5 and 5, or between 0.5 and 1; between 1 and 10, or between 1 and 5; or between 5 and 10. The dual agonists described in the examples below have slightly lower GLP-2 potency than teduglutide and so may, for example, have a relative potency between 0.01 and 1, between 0.01 and 0.5, or between 0.01 and 0.1.

30 By contrast, the dual agonists of the invention have higher potency at the GLP-2 receptor (e.g. the human GLP-2 receptor) than human GLP-1(7-37), liraglutide (NN2211; Victoza), or Exendin-4. Thus, the relative potency of the dual agonists at the GLP-2 receptor compared to human GLP-1(7-37), liraglutide (NN2211; Victoza), or Exendin-4 is greater than 1, typically greater than 5 or greater than 10, and may be
35 up to 100, up to 500, or even higher (if the reference GLP-1 agonist even exerts detectable activity at the GLP-2 receptor).

It will be understood that the absolute potencies of the dual agonists at each receptor are much less important than the balance between the GLP-1 and GLP-2 agonist activities. Thus it is perfectly acceptable for the absolute GLP-1 or GLP-2 potency to be lower than that of known agonists at those receptors, as long as the dual agonist
5 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.

Pharmaceutical compositions

10 An aspect of the present invention relates to a composition comprising a dual agonist according to the invention, or a pharmaceutically acceptable salt or solvate thereof, together with a carrier. In one embodiment of the invention, the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier. The present invention also relates to a pharmaceutical composition comprising a dual
15 agonist according to the invention, or a salt or solvate thereof, together with a carrier, excipient or vehicle. Accordingly, the dual agonist of the present invention, or salts or solvates thereof, especially pharmaceutically acceptable salts or solvates thereof, may be formulated as compositions or pharmaceutical compositions prepared for storage or administration, and which comprise a therapeutically effective amount of a
20 dual agonist of the present invention, or a salt or solvate 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,
25 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
30 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-
35 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.

In one embodiment, a pharmaceutical composition of the invention is one wherein the
5 dual agonist is in the form of a pharmaceutically acceptable acid addition salt.

In some embodiments, the pharmaceutical composition of the invention is formulated as 1 mL solution for injection.

10 In some embodiments, the pharmaceutical composition of the invention is formulated as:

- (i) at least about 1 mg/mL of one or more GLP-1/GLP-2 dual agonist
- (ii) 5 mM to about 50 mM of phosphate buffer component
- (iii) about 190 mM to about 240 mM of mannitol

15 and the pH is about pH 8.0.

In some aspects, the composition of this invention comprises the below listed ingredients:

Component	Function
GLP-1/GLP-2 dual agonist	Drug substance
Phosphate buffer	Buffer component
NaH ₂ PO ₄ Sodium dihydrogen phosphate, anhydrous / Monobasic sodium phosphate, anhydrous	Buffer component
Mannitol (D-mannitol)	Tonicity agent
Hydrochloric acid	pH adjustment
Sodium Hydroxide	pH adjustment
Water for Injections	Solvent

20 wherein the GLP-1/GLP-2 dual agonist is a pharmaceutically acceptable salt of Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIWLIQHKITD-OH (SEQ ID NO: 5).

In some aspects, the composition of this invention comprises the below listed
25 ingredients:

Component	Function
GLP-1/GLP-2 dual agonist	Drug substance
Disodium phosphate, anhydrous / Dibasic sodium phosphate, anhydrous (such as Na ₂ HPO ₄)	Buffer component
NaH ₂ PO ₄ Sodium dihydrogen phosphate, anhydrous / Monobasic sodium phosphate, anhydrous	Buffer component
Mannitol (D-mannitol)	Tonicity agent
Hydrochloric acid	pH adjustment
Sodium Hydroxide	pH adjustment
Water for Injections	Solvent

wherein the GLP-1/GLP-2 dual agonist is a pharmaceutically acceptable salt of Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (SEQ ID NO: 5).

Dosage regime

It will be understood that the dose of the GLP-1/GLP-2 dual agonist and dose of the amylin analogue may be independently selected. The dose of the GLP-1/GLP-2 dual agonist may be selected as described here.

According to the invention, the dual GLP-1/GLP-2 agonists are for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea. The invention comprises methods of administering the dual agonist to the patient at a dose of about 0.1 mg to 10.0 mg.

The dose of about 0.1 mg to 10.0 mg of dual agonist is administered to the patient in a single administration (i.e. a single administration event). In other words, the dual agonist is administered to the patient in a single dosage formulation of about 0.1 mg to about 10.0 mg. This single dosage formulation may be administered to the patient once or multiple times wherein each of the multiple dosage formulations for administration to the patient need not comprise the same amount of the dual agonist. In other words, the dual agonist may be administered to the patient in a series of single administrations wherein each of the single administrations may not comprise

the same amount of the dual agonist. Each administration of the dual agonist to the patient may be independently selected to be at a dose of about 0.1 mg to about 10.0 mg.

- 5 Thus, the invention provides a GLP-1/GLP-2 dual agonist as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, wherein the method comprises at least one administration of
10 the dual agonist to the patient at a dose of about 0.1 mg to 10.0 mg.

Dose

In one aspect the dual agonist is administered to the patient at a dose of from about 0.1 mg to about 10.0 mg. In one aspect the dual agonist is administered to the patient
15 at a dose of from about 1.0 mg to about 10.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 1.1 mg to about 10.0 mg, from about 1.2 mg to about 10.0 mg, from about 1.3 mg to about 10.0 mg, or from about 1.4 mg to about 10.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 1.5 mg to about 10.0 mg. In one aspect the dual agonist is
20 administered to the patient at a dose of from about 1.6 mg to about 10.0 mg, from about 1.7 mg to about 10.0 mg, from about 1.8 mg to about 10.0 mg, or from about 1.9 mg to about 10.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.0 mg to about 10.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.1 mg to about 10.0 mg, or from
25 about 2.2 mg to about 10.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.25 mg to about 10.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 3.0 mg to about 10.0 mg, from about 4.0 mg to about 10.0 mg, from about 5.0 mg to about 10.0 mg, from about 6.0 mg to about 10.0 mg, from about 7.0 mg to about 10.0 mg, from about 8.0
30 mg to about 10.0 mg, or from about 9.0 mg to about 10.0 mg.

In one aspect the dual agonist is administered to the patient at a dose of from about 0.1 mg to about 9.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 1.0 mg to about 9.0 mg. In one aspect the dual agonist is
35 administered to the patient at a dose of from about 1.1 mg to about 9.0 mg, from about 1.2 mg to about 9.0 mg, from about 1.3 mg to about 9.0 mg, or from about 1.4

- mg to about 9.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 1.5 mg to about 9.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 1.6 mg to about 9.0 mg, from about 1.7 mg to about 9.0 mg, from about 1.8 mg to about 9.0 mg, or from about 1.9
- 5 mg to about 9.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.0 mg to about 9.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.1 mg to about 9.0 mg, or from about 2.2 mg to about 9.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.25 mg to about 9.0 mg. In one aspect the dual
- 10 agonist is administered to the patient at a dose of from about 3.0 mg to about 9.0 mg, from about 4.0 mg to about 9.0 mg, from about 5.0 mg to about 9.0 mg, from about 6.0 mg to about 9.0 mg, from about 7.0 mg to about 9.0 mg, or from about 8.0 mg to about 9.0 mg.
- 15 In one aspect the dual agonist is administered to the patient at a dose of from about 0.1 mg to about 8.0 mg. In one aspect the dual agonist is administered to the patient at a dose of about 1.0 mg to about 8.0 mg. In one aspect the dual agonist is administered to the patient at a dose of about 1.1 mg to about 8.0 mg, about 1.2 mg to about 8.0 mg, about 1.3 mg to about 8.0 mg, or about 1.4 mg to about 8.0 mg. In
- 20 one aspect the dual agonist is administered to the patient at a dose of about 1.5 mg to about 8.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 1.6 mg to about 8.0 mg, from about 1.7 mg to about 8.0 mg, from about 1.8 mg to about 8.0 mg, or from about 1.9 mg to about 8.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.0 mg to about 8.0 mg.
- 25 In one aspect the dual agonist is administered to the patient at a dose of from about 2.1 mg to about 8.0 mg, or from about 2.2 mg to about 8.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.25 mg to about 8.0 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 3.0 mg to about 8.0 mg, from about 4.0 mg to about 8.0 mg, from about 5.0 mg
- 30 to about 8.0 mg, from about 6.0 mg to about 8.0 mg, or from about 7.0 mg to about 8.0 mg.
- In one aspect the dual agonist is administered to the patient at a dose of from about 1.0 mg to about 7.5 mg, from about 1.0 mg to about 7.0 mg, from about 1.0 mg to about 6.0 mg, from about 1.0 mg to about 5.0 mg, from about 1.0 mg to about 4.0 mg, or from about 1.0 mg to about 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose of about 1.5 mg to about 7.5 mg. In one aspect the dual
- 35

- agonist is administered to the patient at a dose of from about 1.5 mg to about 7.0 mg, from about 1.5 mg to about 6.0 mg, from about 1.5 mg to about 5.0 mg, from about 1.5 mg to about 4.0 mg, or from about 1.5 mg to about 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose from about 2.0 mg to about 7.5 mg,
- 5 from about 2.0 mg to about 7.0 mg, from about 2.0 mg to about 6.0 mg, from about 2.0 mg to about 5.0 mg, from about 2.0 mg to about 4.0 mg, or from about 2.0 mg to about 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 2.25 mg to about 7.5 mg, from about 2.25 mg to about 7.0 mg, from about 2.25 mg to about 6.0 mg, from about 2.25 mg to about 5.0 mg, from about 2.25
- 10 mg to about 4.0 mg, or from about 2.25 mg to about 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 4.0 mg to about 7.5 mg. In one aspect the dual agonist is administered to the patient at a dose of from about 4.0 mg to about 6.0 mg.
- 15 In one aspect the dual agonist is administered to the patient at a dose of from 1.0 mg to 7.5 mg, from 1.0 mg to 7.0 mg, from 1.0 mg to 6.0 mg, from 1.0 mg to 5.0 mg, from 1.0 mg to 4.0 mg, or from 1.0 mg to 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose of 1.5 mg to 7.5 mg. In one aspect the dual agonist is administered to the patient at a dose of from 1.5 mg to 7.0 mg, from 1.5 mg
- 20 to 6.0 mg, from 1.5 mg to 5.0 mg, from 1.5 mg to 4.0 mg, or from 1.5 mg to 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose from 2.0 mg to 7.5 mg, from 2.0 mg to 7.0 mg, from 2.0 mg to 6.0 mg, from 2.0 mg to 5.0 mg, from 2.0 mg to 4.0 mg, or from 2.0 mg to 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose of from 2.25 mg to 7.5 mg, from 2.25 mg to 7.0
- 25 mg, from 2.25 mg to 6.0 mg, from 2.25 mg to 5.0 mg, from 2.25 mg to 4.0 mg, or from 2.25 mg to 3.5 mg. In one aspect the dual agonist is administered to the patient at a dose of from 4.0 mg to 7.5 mg. In one aspect the dual agonist is administered to the patient at a dose of from 4.0 mg to 6.0 mg.
- 30 In one aspect the dose is more than 0.6 mg. In one aspect the dual agonist is administered to the patient at a dose of about 1.5 mg.
- In some aspects the dual agonist is administered to the patient at a dose of about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.25 mg, about 2.5 mg, about 3.0 mg, about
- 35 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg, about 6.0 mg, about 6.5 mg, about 7.0 mg, about 7.5 mg, about 8.0 mg, about 9.0 mg or about 10.0 mg. In some aspects the dual agonist is administered to the patient at a dose of 1.0

mg, 1.5 mg, 2.0 mg, 2.25 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 9.0 mg or 10.0 mg.

Administration

5 The administration of the dual agonists described herein may be by any mode of administration common or standard in the art, e.g. oral, intravenous, intramuscular, subcutaneous, sublingual, intranasal, intradermal, suppository routes or implanting. In a preferred embodiment of the invention as described herein administration is by subcutaneous injection.

10

The dosage regime of the invention may involve administering more than one dose of the dual agonist. Thus, in some aspects the invention provides a GLP-1/GLP-2 dual agonist as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of reducing or inhibiting weight gain, reducing food intake,
15 reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, wherein the method comprises one or more administrations of the dual agonist to the patient at a dose of about 0.1 mg to 10.0 mg. In some aspects, the method comprises two or more administrations of the dual agonist to the patient at a dose of about 0.1 mg to 10.0
20 mg. In some aspects, each administration of the dual agonist to the patient is at a dose of about 0.1 mg to 10.0 mg.

In some aspects of the invention wherein the method comprises more than one administration of the dual agonist to the patient, the dose of the dual agonist may be
25 different at each administration. In other words, it is not required that the dose of the dual agonist is the same at each administration. However, in other aspects of the invention wherein the method comprises more than one administration of the dual agonist to the patient, the dose of the dual agonist may be the same, or substantially the same, at each administration.

30

For some aspects of the present invention, a series of single administrations are delivered to the patient wherein the initial course of the single administrations may have subsequent increasing dose amounts of the dual agonist in the single dosage formulations. In some aspects, the initial course may include any one of 2, 3, 4, 5, 6,
35 7, 8, 9, 10 or more administrations of increasing amounts of the dual agonist in the single administration formulations. In some aspects, after the initial course the subsequent dose amounts of the dual agonist in the single dosage formulations may

be the same as the last dose of the initial course or may be less than the dose of the last dose of the initial course or may be higher than the last dose of the initial course. In certain aspects, after the initial course the subsequent dose amounts of the dual agonist in the single dosage formulations may be the same or about the same as the
5 last dose of the initial course.

The administration may involve weekly administration of the dual agonist. The reference to "weekly" is intended to mean approximately every 7 days, for example, approximately every 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 or 9 days with each "day" being
10 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. 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. In one aspect of the invention described herein the reference to
15 "weekly" may mean 7 days $\pm$ 2 days. That is to say the administration may take place either up to and including two days before, or up to and including two days after the stated day. As such, the administration may take place 2 or 1 days before, or 1 or 2 days after, the stated day. In one aspect, the dual agonist is administered weekly at a dose of from about 1.5 mg to about 10.0 mg, such as from about 1.5 mg to about 7.5
20 mg, such as from about 1.5 mg to about 6.0 mg, such as from about 1.5 mg to about 4.0 mg, such as from about 1.5 mg to about 3.5 mg. In one aspect, the dual agonist is administered weekly at a dose of from about 2.0 mg to about 7.5 mg, such as from about 2.0 mg to about 6.0 mg, such as from about 2.0 mg to about 4.0 mg, such as from about 2.0 mg to about 3.5 mg. In one aspect, the dual agonist is administered
25 weekly at a dose of from about 2.25 mg to about 3.5 mg. In one aspect, the dual agonist is administered weekly at a dose of from 1.5 mg to 10.0 mg, such as from about 1.5 mg to about 7.5 mg, such as from 1.5 mg to 6.0 mg, such as from 1.5 mg to 4.0 mg, such as from 1.5 mg to 3.5 mg. In one aspect, the dual agonist is administered weekly at a dose of from 2.0 mg to 7.5 mg, such as from 2.0 mg to 6.0
30 mg, such as from 2.0 mg to 4.0 mg, such as from 2.0 mg to 3.5 mg. In one aspect, the dual agonist is administered weekly at a dose of from 2.25 mg to 3.5 mg.

In one aspect the number of doses administered to a patient may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more doses. In other words, in some aspects the dual agonist is
35 administered to the patient 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more times. In some aspects, the method comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more administrations of the dual agonist. In some aspects the dual agonist is administered

- to the patient 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more times at a dose of about 0.1 to 10.0 mg (or at any other dose described herein). In some aspects, the method comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more administrations of the dual agonist at a dose of about 0.1 to 10.0 mg (or at any other dose described herein). In
- 5 one aspect, 4 doses are administered to a patient. In one aspect, the method comprises 4 administrations of the dual agonist at a dose of about 0.1 to 10.0 mg (or at any other dose described herein). In one aspect, 12 doses are administered to a patient. In one aspect, the method comprises 12 administrations of the dual agonist at a dose of about 0.1 to 10.0 mg (or at any other dose described herein).
- 10 In one aspect the agonist may be administered at the same dose each time. In one aspect, each administration to the patient of the dual agonist is at a dose of about 0.1 mg to 10.0 mg.
- 15 In one aspect a number of doses are administered to a patient over a period of weeks, or months or for 1 year or more than 1 year.
- In one aspect a number of doses are administered to a patient weekly and over a period of weeks, or months or for 1 year or more than 1 year.
- 20 In one aspect the agonist may be administered in ascending doses.

Titration and treatment

- The dose of dual agonist according to the invention may be a titration dose or a
- 25 treatment dose.
- The term "titration dose" refers to the dose of the dual agonist administered to the patient at each administration during the titration period, prior to administrations at the treatment dose. Each titration dose is in an amount of 0.1 mg to 10.0 mg of the dual
- 30 agonist. The doses, dosage regime and administration protocols presented herein equally apply to the titration dose(s).
- The term "treatment dose" refers to the dose of the dual agonist administered to the patient at each administration during the treatment period. Each treatment dose is in
- 35 an amount of 0.1 mg to 10.0 mg of the dual agonist. The doses, dosage regime and administration protocols presented herein equally apply to the treatment dose(s).

In some aspects, the dual agonist is administered to the patient according to a titration regimen. 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.

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 period, allowing a physician to observe side-effects at different doses and thereby determine an appropriate dose for treatment.

Thus, in some aspects the invention provides a GLP-1/GLP-2 dual agonist as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, wherein the method comprises at least one administration of the dual agonist to the patient at a dose of about 0.1 mg to 10.0 mg, and wherein the method comprises at least one administration of the dual agonist to the patient at a titration dose and at least one administration of the dual agonist to the patient at a treatment dose. In other words, in some aspects the method comprises administering the dual agonist to the patient at least once at a titration dose and at least once at a treatment dose.

In some aspects, the method comprises more than one administration (i.e. 2 or more administrations) of the dual agonist to the patient at a titration dose. In some aspects, the method comprises 3 or more, 4 or more or 5 or more administrations of the dual agonist to the patient at a titration dose. In some aspects, the method comprises 1, 2, 3, 4 or 5 administrations of the dual agonist to the patient at a titration dose. In preferred aspects, the method comprises 2 administrations of the dual agonist to the patient at a titration dose. In preferred aspects, the method comprises 5 administrations of the dual agonist to the patient at a titration dose.

In one aspect there may be at least one initial titration period of a lower dose prior to increasing the dose. In one aspect the titration period may constitute 1, 2, 3, or 4 doses of a lower dose, wherein preferably the doses are the same each time. In one aspect the titration period consists of 1 dose of a lower dose. In one aspect the
5 titration period consists of 2 doses of a lower dose.

In a preferred aspect the titration doses are administered weekly. In other words, in some aspects the method comprises administering the dual agonist to the patient once weekly at a titration dose.

10

The titration dose may be any dose of dual agonist as described elsewhere herein. In some aspects titration dose is from about 0.1 mg to about 10.0 mg. In some aspects the titration dose is from about 1.0 mg to about 6.0 mg, for example from about 1.5 mg to about 6.0 mg. Thus, in some aspects the method comprises at least one
15 administration of the dual agonist to the patient at a titration dose of from about 1.5 mg to about 6.0 mg. In one aspect the titration dose is from about 1.0 mg to about 4.0 mg, for example from about 1.5 mg to about 4.0 mg. In one aspect the titration dose is about 1.0 mg to about 3.5 mg, for example about 1.5 mg to about 3.5 mg, or about 1.5 mg to about 3.0 mg. In one aspect the titration dose is or is about 1.0 mg, 2.0 mg,
20 2.25 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg or 6.0 mg. In some aspects the titration dose is 2.0 mg. In some aspects the titration dose is 2.0 mg administered once weekly. In some aspects the titration dose is 4.0 mg. In some aspects the titration dose is 4.0 mg administered once weekly.

25 The titration dose is not required to be the same at each administration. In other words, different titration doses may be administered to the patient within the titration period. Thus, in some aspects the invention provides a GLP-1/GLP-2 dual agonist as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite,
30 promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, wherein the method comprises at least one administration of the dual agonist to the patient at a dose of about 0.1 mg to 10.0 mg, and wherein the method comprises at least one administration of the dual agonist to the patient at one or more titration doses and at least one administration of the dual
35 agonist to the patient at a treatment dose.

In some aspects, the method comprises 2 or more, 3 or more, or 4 or more different titration doses. In some aspects, the method comprises 2, 3, or 4 different titration doses. In preferred aspects, the method comprises 2 different titration doses. Each titration dose may be any of the doses of dual agonist described elsewhere herein.

5

In some aspects, all titration doses are the same (i.e. there is one titration dose, which is the same for all administrations of the dual agonist to the patient in the titration period).

- 10 In some aspects, the method comprises one administration of the dual agonist to the patient at a titration dose of 3.5 mg. In some aspects, the method comprises two administrations of the dual agonist to the patient at a titration dose of 2.0 mg. In some aspects, the method comprises two administrations of the dual agonist to the patient at a titration dose of 2.0 mg and three administrations of the dual agonist to the
- 15 patient at a titration dose of 4.0 mg.

- In some aspects, the method comprises more than one administration (i.e. 2 or more administrations) of the dual agonist to the patient at a treatment dose. In some aspects, the method comprises 3 or more, 4 or more, 5 or more, 6 or more, 7 or more,
- 20 8 or more, 9 or more, 10 or more, 11 or more, or 12 or more administrations of the dual agonist to the patient at a treatment dose. In some aspects, the method comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 administrations of the dual agonist to the patient at a treatment dose. In preferred aspects, the method comprises 3 administrations of the dual agonist to the patient at a treatment dose. In preferred
- 25 aspects, the method comprises 10 administrations of the dual agonist to the patient at a treatment dose. In preferred aspects, the method comprises 7 administrations of the dual agonist to the patient at a treatment dose.

- The treatment dose may continue to be administered for as long as is necessary. The
- 30 dual agonist at a treatment dose may be administered to the patient for a period of, for example, one month to twenty years, for example for a period of one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, two years, three years, four years, five years, six years, seven years, eight years, nine years, ten years,
- 35 eleven years, twelve years, thirteen years, fourteen years, fifteen years, sixteen years, seventeen years, eighteen years, nineteen years or twenty years.

For example, the treatment dose may be administered weekly to the patient for a period of, for example, one month to twenty years, for example for a period of one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, two years, 5 three years, four years, five years, six years, seven years, eight years, nine years, ten years, eleven years, twelve years, thirteen years, fourteen years, fifteen years, sixteen years, seventeen years, eighteen years, nineteen years or twenty years.

The treatment dose may be any dose of dual agonist described herein. In some 10 aspects, the treatment dose is from about 0.1 mg to about 10.0 mg. In some aspects the treatment dose is from about 1.0 mg to about 10.0 mg, from about 1.5 mg to about 10.0 mg, from about 2.0 mg to about 10.0 mg, from about 2.25 mg to about 10.0 mg, from about 3.0 mg to about 10.0 mg, from about 4.0 mg to about 10.0 mg, from about 5.0 mg to about 10.0 mg, from about 6.0 mg to about 10.0 mg, from about 7.0 mg to about 10.0 mg, from about 8.0 mg to about 10.0 mg, or from about 9.0 mg 15 to about 10.0 mg. In some aspects the treatment dose is about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.25 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg, about 6.0 mg, about 6.5 mg, about 7.0 mg, about 7.5 mg, about 8.0 mg, about 9.0 mg or about 10.0 mg. In some aspects 20 the treatment dose is 1.0 mg, 1.5 mg, 2.0 mg, 2.25 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 9.0 mg or 10.0 mg.

Typically, in aspects wherein the dual agonist is administered to the patient at the 25 treatment dose more than once (i.e. multiple administrations of the dual agonist at the treatment dose) all administrations in the treatment period are at the same dose. Thus, in some aspects, all treatment doses are the same (i.e. there is one treatment dose, which is the same for all administrations of the dual agonist to the patient in the treatment period).

30 However, the treatment dose is not required to be the same at each administration. In other words, different treatment doses may be administered to the patient within the treatment period. The treatment dose may be varied in accordance with the patient's response to the dual agonist. For example, if the patient develops severe side-effects 35 at a given treatment dose, the treatment dose may be lowered at future administrations to reduce the severity of the side-effects.

Thus, in some aspects the invention provides a GLP-1/GLP-2 dual agonist as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, promoting weight loss, or treating obesity, morbid obesity, obesity-linked gallbladder disease, or obesity-induced sleep apnea, wherein the method comprises at least one
5 administration of the dual agonist to the patient at a dose of about 0.1 mg to 10.0 mg, and wherein the method comprises at least one administration of the dual agonist to the patient at one or more titration doses and at least one administration of the dual agonist to the patient one or more treatment doses.

10

In some aspects, the method comprises 2 or more, 3 or more, or 4 or more different treatment doses. In some aspects, the method comprises 2, 3, or 4 different treatment doses. Each treatment dose may be any of the doses of dual agonist described elsewhere herein.

15

Typically, the treatment dose is higher than the titration dose. Thus, in some aspects, the treatment dose is higher than the titration dose. In some aspects, the treatment dose is higher than some or all of the titration doses.

20

However, the treatment dose may be lower than the titration dose. This may be the case, for example, where the titration dose is increased as the titration period progresses (i.e. the titration dose becomes higher over successive administrations) but then the dose is decreased for the treatment dose in view of side-effects experienced by the patient as the titration dose increased. Thus, in some aspects, the
25 treatment dose is lower than the titration dose. In some aspects, the treatment dose is lower than some or all of the titration doses.

30

As described herein, a purpose of titration doses is to identify an appropriate treatment dose. Thus, in some aspects the treatment dose is determined by a physician observing the effects of the titration dose on patients. In other words, the treatment dose may depend on the titration dose.

35

In a preferred aspect the treatment doses are administered weekly. In other words, in some aspects the method comprises administering the dual agonist to the patient once weekly at a treatment dose. In some aspects, the method comprises administering the dual agonist to the patient once weekly at a titration dose and once weekly at a treatment dose. In other words, the once weekly administration of the dual

agonist at the treatment dose is a continuation of the once weekly administrations at the titration dose.

5 In one aspect the titration period may be followed by one or more doses at a higher dose than the titration dose. In one aspect the titration period is followed by 1, 2, 3 or 4 doses at a higher dose than the titration dose. In one aspect the titration period is followed by 3 doses at a higher dose than the titration dose. In one aspect the titration period is followed by 10 doses at a higher dose than the titration dose. In one aspect the titration period is followed by 7 doses at a higher dose than the titration dose. In
10 one aspect the titration period consists of 1 dose and is followed by 3 doses at a higher dose than the titration dose. In one aspect the titration period consists of 2 doses and is followed by 10 doses at a higher dose than the titration dose. In one aspect the higher dose is between about 3 mg to about 8 mg. In one aspect the higher dose is from about 3 mg to about 8 mg.

15 In some aspects, the method comprises one administration of the dual agonist to the patient at a titration dose of 3.5 mg and three administrations of the dual agonist to the patient at a treatment dose of 6.0 mg, wherein each administration is once weekly.

20 In some aspects, the method comprises two administrations of the dual agonist to the patient at a titration dose of 2.0 mg and ten administrations of the dual agonist to the patient at a treatment dose of 4.0 mg, wherein each administration is once weekly.

25 In some aspects, the method comprises two administrations of the dual agonist to the patient at a titration dose of 2.0 mg, three administrations of the dual agonist to the patient at a titration dose of 4.0 mg, and seven administrations of the dual agonist to the patient at a treatment dose of 6.0 mg, wherein each administration is once weekly.

30 In one aspect the higher dose (following the titration period) is or is about 6.0 mg, 7.0 mg, 7.5 mg or 8.0 mg, preferably 6.0 mg.

The titration doses may be administered daily, every other day or weekly.

35 The post-titration doses are administered daily, every other day, or 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.

5 In one aspect there may be more than one titration period.

In one aspect of the invention further doses are administered after the doses discussed above, i.e. the subject may continue to receive doses after the initial doses discussed herein.

10

Additional dosing may be once weekly.

Administration of the dual agonist may continue as long as necessary.

15 Additional doses as described above may be administered as required for a period of, for example, one month to twenty years, for example for a period of one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, two years, three years, four years, five years, six years, seven years, eight years, nine years, ten years,
20 eleven years, twelve years, thirteen years, fourteen years, fifteen years, sixteen years, seventeen years, eighteen years, nineteen years or twenty years.

In a preferred aspect, the dual agonist is administered to the subject on a daily basis.

25 **Medical conditions**

The dual agonists described in this specification have biological activities of both GLP-1 and GLP-2.

30 GLP-1 is a peptide hormone known for its important role in glucose homeostasis. When secreted from the gastrointestinal tract in response to nutrient ingestion, GLP-1 potentiates glucose-stimulated insulin secretion from the 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).

35

Besides the primary actions of GLP-1 on glucose-stimulated insulin secretion, GLP-1 is also 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
5 (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, participating in glucose homeostasis and lipid metabolism in tissues such as muscle, liver, and adipose tissues (Kim and Egan, 2008, *Pharmacol.Rev.* 470-512).

10

In combination with the amylin analogue, the dual agonist compounds described herein also find use, *inter alia*, in reducing or inhibiting weight gain, reducing rate of gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss. The effect on body weight may be mediated in part or wholly
15 via reducing food intake, appetite or intestinal transit.

Thus the dual agonists of the invention can be used for the prophylaxis or treatment of obesity, morbid obesity, obesity-linked gallbladder disease and obesity-induced sleep apnea.

20

Independently of their effect on body weight, the dual agonists of the invention may have a beneficial effect on glucose tolerance and/or glucose control. They may also be used to modulate (e.g. improve) circulating cholesterol levels, being capable of lowering circulating triglyceride or LDL levels, and increasing HDL/LDL ratio.

25

Thus, they may be used for the prophylaxis or treatment of inadequate glucose control, glucose tolerance or dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio) and associated conditions, including diabetes (e.g. Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome and hypertension.

30

Many of these conditions are also associated with obesity or overweight. The effects of the dual agonists on these conditions may therefore follow from their effect on body weight, in whole or in part, or may be independent thereof.

35 Effects on body weight may be therapeutic or cosmetic.

The dual agonist activity of the compounds described herein may be particularly beneficial in many of the conditions described, as the two activities may complement one another.

- 5 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
- 10 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.

15

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

- As mentioned above, 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
- 20 the insult arises. The inflammatory response may be acute (short lived) or chronic (longer lasting).

- It has been demonstrated that, e.g., obese mice (ob/ob and db/db mice) have a disrupted mucosal barrier function and exhibit increased low-grade inflammation (Brun et al., 2007, Am. J. Physiol. Gastrointest. Liver Physiol., 292: G518-G525, Epub
- 30 5 Oct 2006). These observations were further extended to C57BL6/J mice maintained on a high-fat diet (Cani et al., 2008, Diabetes, vol. 57, 1470-1481) and to non-obese diabetic mice (Hadjiyanni et al., 2009, Endocrinology, 150(2): 592–599).

- 35 Cani and colleagues (Gut; 2009, 58:1091-1103,) reported that in ob/ob mice, the modulation of the gut microbiota resulted in decreased intestinal barrier dysfunction

and reduced systemic inflammation via a GLP-2 dependent pathway. Further, the increased intestinal permeability observed in obese and diabetic patients is likely to play a more vital role in the disease progression than previously anticipated.

Increased intestinal permeability leads to increased bacterial lipopolysaccharide (LPS) transport across the intestinal barrier. This increased LPS activates immune cells, such as circulating macrophages and macrophages residing in organs in the body, causing low-grade chronic inflammation that may be involved in the pathogenesis of many diseases. This phenomenon is called metabolic endotoxemia (ME).

10

The inflammatory process may also play a role in causing metabolic dysfunction in obese individuals, such as insulin resistance and other metabolic disturbances.

Thus the dual agonist compounds of the invention may be particularly useful for prophylaxis or treatment of low grade inflammation, especially in obese or overweight individuals, exerting beneficial effects via the GLP-1 agonist component of their activity and/or the GLP-2 component of their activity.

The therapeutic efficacy of treatment with a dual agonist of the invention may be monitored by enteric biopsy to examine the villus morphology, by biochemical assessment of nutrient absorption, by non-invasive determination of intestinal permeability, by patient weight gain, or by amelioration of the symptoms associated with these conditions.

25 Amylin analogues

The amylin analogues (which may also be referred to as compounds or peptides) may suitably be manufactured by standard synthetic methods. Thus, the peptides may be synthesized by, e.g., 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 positions 2 and 7, e.g. as described below. 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.

35

Amylin analogues according to the invention may have the formula:

R^1 -Z- R^2

Wherein:

5

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

10

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

15 NO: 8)

wherein:

- X1 is selected from the group consisting of Arg, Lys and Glu;
- X3 is selected from the group consisting of Gly, Gln and Pro;
- 20 • 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;
- X14 is selected from the group consisting of Aad, His, Asp, Asn and Arg;
- 25 • 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;
- 30 • X35 is selected from the group consisting of Asn and Ser;
- X37 is selected from the group consisting of Hyp and Pro; and
- X2 and X7 are amino acid residues whose side chains together form a lactam bridge;
- Gly(Me) is N-methylglycine [also known as sarcosine (Sar)]
- 35 • 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; or a pharmaceutically acceptable salt or solvate thereof.

5 In a preferred embodiment, the amylin analogue is:
[19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-
LSSTEVGST-Hyp-NH₂ (SEQ ID NO: 6).

wherein:

- | | | |
|----|---------------|--|
| 10 | Gly(Me): | N-methylglycine [also known as sarcosine (Sar)] |
| | Ile(Me): | N-methylisoleucine |
| | Aad: | 2-aminoadipic acid, e.g. (2S)-2-aminoadipic acid [also (2S)-2-aminohexanedioic acid], also known as homo-glutamic acid |
| | Hyp: | 4-hydroxyproline, e.g. (2S,4R)-4-hydroxyproline |
| 15 | | [also denoted (4R)-4-hydroxy-L-proline] |
| | [19CD]-isoGlu | 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 |
| 20 | | attached to the alpha amino group of the Glu linker via an amide linkage (as described below). |

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

30 The amylin analogue may be in the form of a pharmaceutically acceptable salt or solvate, such as a pharmaceutically acceptable acid addition salt.

Half-life extending moieties M

35 As described herein, the N-terminal moiety R¹ in a compound of the invention may be 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 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.

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 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 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 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 eicosanoyl group. Examples of functionalized hydrocarbon chains are 15-carboxy-pentadecanoyl, 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, three or more linked sub-moieties L¹, L², L³, ..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 selected from acyl, sulfonyl, an N atom, an O atom and an S atom. The linker may consist of a linear or branched C₁₋₁₀ hydrocarbon chain or more preferably a linear C₁₋₅ hydrocarbon chain. Furthermore, the linker can be substituted with one or more substituents selected from C₁₋₆ alkyl, amino C₁₋₆ alkyl, hydroxy C₁₋₆ alkyl and carboxy C₁₋₆ alkyl.

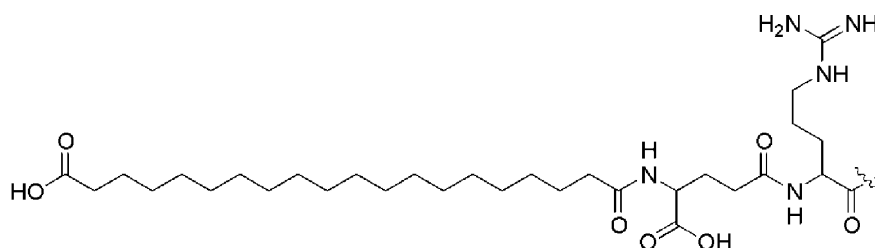
In some embodiments the linker may comprise one or more (e.g. one, two or three) linked amino acid residues, which may each independently be a residue of any naturally occurring or non-naturally occurring amino acid. For example, the linker may comprise one, two or three linked amino acid residues, each 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, β-Asp, Ser, Thr, Gaba, Aib, β-Ala (i.e. 3-aminopropanoyl), 4-aminobutanoyl, 5-aminopentanoyl, 6-aminohexanoyl, 7-aminohexanoyl, 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 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.

Linkers consisting of isoGlu and isoGlu-isoGlu may be particularly preferred.

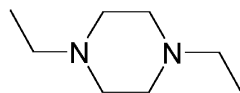
An example of a lipophilic substituent comprising a lipophilic moiety M and linker L is shown in the formula below:



- 5 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 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
- 10 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.

- The skilled person will be well aware of suitable techniques for preparing the
- 15 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).

- 20 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
- 25 below:

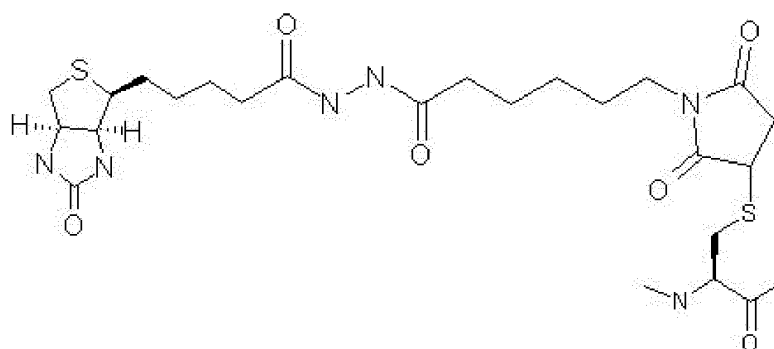


- In some embodiments, the cycloalkane or heterocycloalkane moiety is a six-
- 30 membered ring, e.g. a piperidine ring.

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



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.

Efficacy of compounds

The compounds of the invention are amylin receptor agonists, i.e. they are capable of binding to, and inducing signaling by, one or more receptors or receptor complexes regarded as physiological receptors for human amylin. These 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 hAMYP1, hAMYP2 and hAMYP3 (i.e. human amylin receptors 1, 2 and 3) respectively.

5

A compound may be considered an amylin receptor agonist if it has agonist activity at one or more of hAMYP1, hAMYP2 and hAMYP3, e.g. against hAMYP1 and/or hAMYP3, e.g. at hAMYP3.

- 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 hAMYP1, hAMYP2 and hAMYP3 (i.e. its activity at all of these receptors) in a
- 15 comparable assay. Agonist activity at hCT-R may be less than 5-fold higher than agonist activity at hAMYP1, hAMYP2 and hAMYP3, substantially equal to (e.g. +/- 10%) agonist activity at hAMYP1, hAMYP2 and hAMYP3, or less than agonist activity at hAMYP1, hAMYP2 and hAMYP3. In this regard, it may be sufficient just to compare activity between hCT-R and hAMYP3.

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

25 calcium release, β -arrestin recruitment, receptor internalization, kinase activation or inactivation, lipase activation, inositol phosphate release, diacylglycerol release or nuclear transcription factor translocation.

- A suitable comparable assay format would utilize cells which express hCT-R and
- 30 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 hAMYP1, hAMYP2 and hAMYP3 (i.e. hCT-R plus one of hRAMP1, hRAMP2 and hRAMP3), e.g. hAMYP3. The base cells will typically be mammalian cells and may be primate
- 35 cells. They may be non-human primate cells. 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.

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

Compounds of the present invention may exhibit a number of advantageous properties in relation to human amylin and existing analogues thereof, such as
10 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 one or more of the receptors hCT-R, hAMYR1, hAMYR2 or hAMYR3. Additionally, or alternatively, compounds of the
15 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, especially at pH values in the range from 4 to 7, or at a range of pH values across
20 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, compounds of the invention may be thus well suited for co-formulation with, for example, insulin,
30 various insulin analogues and/or other therapeutic (e.g. anti-diabetic or anti-obesity) agents that require a neutral or near-neutral formulation pH.

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
35 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 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.

5 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 make use of the mature protein, lacking the signal sequence.

10

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 having EC₅₀ [hCT-R] lower than the EC₅₀ [hCT-R] of native
15 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-
20 R is below 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 0.9 nM (e.g. 0.001 to 0.9 nM).

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

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

30

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

35 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 below 1.0 nM (e.g. 0.001 to 1.0 nM).

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

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

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

20 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 and hAMYR3, e.g. at hAMYR3.

25 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.

30 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.

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.

35

Therapeutic uses

In combination with the dual agonists, the amylin analogues are useful, *inter alia*, in the reduction of food intake, promotion of weight loss, and inhibition or reduction of weight gain. They may therefore provide an attractive treatment option for, *inter alia*,
5 obesity and metabolic diseases caused, characterised by, or associated with, excess body weight. Thus, the compounds may be used in a method of treating, inhibiting or reducing weight gain, promoting weight loss, reducing food intake, and/or reducing excess body weight. Treatment may be achieved, for example, by control of appetite, feeding, food intake, calorie intake and/or energy expenditure.

10

The compounds may be used in a method of treating obesity as well as associated diseases, disorders and health conditions, including, but not limited to, morbid obesity, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease and obesity-induced sleep apnea and respiratory problems,
15 degeneration of cartilage, osteoarthritis, and reproductive health complications of obesity or overweight such as infertility.

The compounds may also be used in a method of prevention or treatment of Alzheimer's disease, diabetes, type 1 diabetes, type 2 diabetes, pre-diabetes, insulin
20 resistance syndrome, impaired glucose tolerance (IGT), disease states associated with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, hypertension, atherogenic dyslipidemia, hepatic steatosis ("fatty liver"; including non-alcoholic fatty liver disease (NAFLD), which itself includes non-alcoholic steatohepatitis (NASH)), kidney failure, arteriosclerosis (e.g. atherosclerosis),
25 macrovascular disease, microvascular disease, diabetic heart disease (including diabetic cardiomyopathy and heart failure as a diabetic complication) coronary heart disease, peripheral artery disease or stroke.

The compounds may also be useful in lowering circulating LDL levels and/or
30 increasing HDL/LDL ratio.

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.

35 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
5 in the blood).

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
10 appears to be abdominal obesity.

Pharmaceutical compositions

The invention also extends to compositions, such as pharmaceutical compositions, comprising the amylin analogues. As with all aspects of the invention, it is to be
15 understood that reference to an amylin analogue encompasses reference to pharmaceutically acceptable salts and solvates.

The amylin analogues of the present invention may be formulated as pharmaceutical compositions which are suited for administration with or without storage, and which
20 typically comprise a therapeutically effective amount of at least one peptide of the invention, together with a pharmaceutically acceptable carrier, excipient or vehicle.

The term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical carriers. Pharmaceutically acceptable carriers for therapeutic use are
25 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, 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,
30 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 encompasses any carrier agents listed in the US Pharmacopeia for use in animals, including humans.

35

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 component or components. The unit dosage form may be presented as a packaged preparation, the package containing discrete quantities of the preparation, 5 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 form, for example in the form of a pen device containing a liquid-phase (typically aqueous) composition. Compositions may be 10 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 transdermal) administration or administration by inhalation. The formulations may conveniently be 15 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 peptides of the invention.

20 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, 25 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.

Still further embodiments relate to oral formulations and oral administration. 30 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 35 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.

Dosages

10 It will be understood that the dose of the GLP-1/GLP-2 dual agonist and dose of the amylin analogue may be independently selected. The dose of the amylin analogue may be selected as described here.

15 A typical dosage of an amylin analogue as employed in the context of the present invention may be in the range from about 0.0001 to about 100 mg/kg body weight per day or every other day, such as from about 0.0005 to about 50 mg/kg body weight per day or every other day, such as from about 0.001 to about 10 mg/kg body weight per day or every other day, e.g. from about 0.01 to about 1 mg/kg body weight per day or every other day, administered in one or more doses, such as from one to three doses.

20 The exact dosage employed will depend, *inter alia*, on: 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 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.

25 A typical dosage of an amylin analogue as employed in the context of the present invention may be in the range from about 0.5 mg to about 10.0 mg per day or every other day, about 0.6 mg to about 7.5 mg per day or every other day, preferably about 1.2 mg to about 7.5 mg per day or every other day, preferably about 1.2 to about 6.0

30 mg per day or every other day, preferably about 2.4 to about 6.0 mg per day or every other day, preferably about 2.4 to about 4.0 mg per day or every other day, preferably about 2.4 to about 3.5 mg per day or every other day.

35 An amylin analogue of the invention may be administered continuously (e.g. by intravenous administration or another continuous drug administration method), or may be administered to a subject at intervals, typically at regular time intervals, depending

on the desired dosage and the pharmaceutical composition selected by the skilled practitioner for the particular subject. Regular administration dosing intervals include, e.g., once daily, twice daily, once every two, three, four, five or six days, once or twice weekly, once or twice monthly, and the like. Such regular peptide administration

5 regimens may, in certain circumstances such as, e.g., during chronic long-term administration, be advantageously interrupted for a period of time so that the medicated subject reduces the level of, or stops taking, the medication, often referred to as taking a "drug holiday." Drug holidays are useful for, e.g., maintaining or regaining sensitivity to a drug especially during long-term chronic treatment, or to

10 reduce unwanted side-effects of long-term chronic treatment of the subject with the drug. The timing of a drug holiday depends on the timing of the regular dosing regimen and the purpose for taking the drug holiday (e.g., to regain drug sensitivity and/or to reduce unwanted side effects of continuous, long- term administration). In some embodiments, the drug holiday may be a reduction in the dosage of the drug

15 (e.g. to below the therapeutically effective amount for a certain interval of time). In other embodiments, administration of the drug is stopped for a certain interval of time before administration is started again using the same or a different dosing regimen (e.g. at a lower or higher dose and/or frequency of administration). A drug holiday of the invention may thus be selected from a wide range of time-periods and dosage

20 regimens. An exemplary drug holiday is two or more days, one or more weeks, or one or more months, up to about 24 months of drug holiday. So, for example, a regular daily dosing regimen with a peptide of the invention may, for example, be interrupted by a drug holiday of a week, or two weeks, or four weeks, after which time the preceding, regular dosage regimen (e.g. a daily or a weekly dosing regimen) is

25 resumed. A variety of other drug holiday regimens are envisioned to be useful for administering peptides of the invention.

Thus, the peptide may be delivered via an administration regime which comprises two or more administration phases separated by respective drug holiday phases.

30

During each administration phase, the peptide is administered to the recipient subject in a therapeutically effective amount according to a pre-determined administration pattern. The administration pattern may comprise continuous administration of the drug to the recipient subject over the duration of the administration phase.

35 Alternatively, the administration pattern may comprise administration of a plurality of doses of the peptide to the recipient subject, wherein said doses are spaced by dosing intervals.

A dosing pattern may comprise at least two doses per administration phase, at least five doses per administration phase, at least 10 doses per administration phase, at least 20 doses per administration phase, at least 30 doses per administration phase, or more.

Said dosing intervals may be regular dosing intervals, which may be as set out above, including once daily, twice daily, once every two, three, four, five or six days, once or twice weekly, once or twice monthly, or a regular and even less frequent dosing interval, depending on the particular dosage formulation, bioavailability, and pharmacokinetic profile of the peptide.

An administration phase may have a duration of at least two days, at least a week, at least 2 weeks, at least 4 weeks, at least a month, at least 2 months, at least 3 months, at least 6 months, or more.

Where an administration pattern comprises a plurality of doses, the duration of a possible following drug holiday phase is longer than the dosing interval used in that administration pattern. Where the dosing interval is irregular, the duration of a drug holiday phase may be greater than the mean interval between doses over the course of the administration phase. Alternatively, the duration of the drug holiday may be longer than the longest interval between consecutive doses during the administration phase.

The duration of a possible drug holiday phase may be at least twice that of the relevant dosing interval (or mean thereof), at least 3 times, at least 4 times, at least 5 times, at least 10 times, or at least 20 times that of the relevant dosing interval or mean thereof.

Within these constraints, a drug holiday phase may have a duration of at least two days, at least a week, at least 2 weeks, at least 4 weeks, at least a month, at least 2 months, at least 3 months, at least 6 months, or more, depending on the administration pattern during the previous administration phase.

An administration regime entailing the use of drug holiday comprises at least 2 administration phases. Consecutive administration phases are separated by respective drug holiday phases. Thus the administration regime may comprise at

least 3, at least 4, at least 5, at least 10, at least 15, at least 20, at least 25, or at least 30 administration phases, or more, each separated by respective drug holiday phases.

- 5 Consecutive administration phases may utilise the same administration pattern, although this may not always be desirable or necessary. However, if other drugs or active agents are administered in combination with a peptide of the invention, then typically the same combination of drugs or active agents is given in consecutive administration phases. In certain embodiments, the recipient subject is a human.

10

In a preferred aspect, the amylin analogue is administered to the subject every other day.

Medical conditions

- 15 The formulations of the invention are useful, *inter alia*, in the reduction of food intake, promotion of weight loss, and inhibition or reduction of weight gain. They may therefore provide an attractive treatment option for, *inter alia*, obesity and metabolic diseases caused, characterised by, or associated with, excess body weight.

- 20 Thus, the formulations may be used in a method of treating, inhibiting or reducing weight gain, promoting weight loss, reducing food intake, and/or reducing excess body weight. Treatment may be achieved, for example, by control of appetite, feeding, food intake, calorie intake and/or energy expenditure.

- 25 The formulations may be used in a method of treating obesity as well as associated diseases, disorders and health conditions, including, but not limited to, morbid obesity, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease and obesity-induced sleep apnea and respiratory problems, degeneration of cartilage, osteoarthritis, and reproductive health complications of
30 obesity or overweight such as infertility.

- The formulations may also be used in a method of prevention or treatment of Alzheimer's disease, diabetes, type 1 diabetes, type 2 diabetes, pre-diabetes, insulin resistance syndrome, impaired glucose tolerance (IGT), disease states associated
35 with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, hypertension, atherogenic dyslipidemia, hepatic steatosis ("fatty liver";

including non-alcoholic fatty liver disease (NAFLD), which itself includes non-alcoholic steatohepatitis (NASH)), kidney failure, arteriosclerosis (e.g. atherosclerosis), macrovascular disease, microvascular disease, diabetic heart disease (including diabetic cardiomyopathy and heart failure as a diabetic complication) coronary heart
5 disease, peripheral artery disease or stroke.

The formulations may also be useful in lowering circulating LDL levels and/or increasing HDL/LDL ratio.

10 These effects 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
15 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
20 in the blood).

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
25 appears to be abdominal obesity.

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
30 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
35 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.

10 Devices and kits

In some embodiments, the invention relates to a device comprising an amylin analogue or pharmaceutical composition of the invention and/or a dual agonist or pharmaceutical composition of the invention, for delivery of the analogue to a subject. Via such devices, the dual agonists and/or amylin analogues 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.

In some embodiments, the invention relates to a kit comprising a dual agonists and/or an amylin analogue of the invention or a pharmaceutical composition of the invention. In certain embodiments, the kit further comprises packaging and/or instructions for use.

25 Pharmaceutical Compositions and Administration

An aspect of the present invention relates to separate compositions, wherein a first composition comprises a GLP-1/GLP-2 dual agonist according to the invention and/or a pharmaceutically acceptable salt or solvate thereof, together with a carrier and the second composition comprises an amylin analogue according to the invention and/or a pharmaceutically acceptable salt or solvate thereof, together with a carrier. The first composition and the second composition may be prepared for storage or administration, and which comprise a therapeutically effective amount of the GLP-1/GLP-2 dual agonist and, separately, the amylin analogue of the present invention, or a salt or solvate thereof.

In one embodiment, a pharmaceutical composition of the invention is one wherein the dual agonist is in the form of a pharmaceutically acceptable acid addition salt; and wherein the pharmaceutical composition optionally comprises one or more
5 pharmaceutically acceptable carrier(s), diluent(s) or excipient(s). This pharmaceutical composition is sometimes referred to as the dual agonist pharmaceutical composition or the dual agonist medicament.

In one embodiment, a pharmaceutical composition of the invention is one wherein the
10 amylin analogue is in the form of a pharmaceutically acceptable acid addition salt; and wherein the pharmaceutical composition optionally comprises one or more pharmaceutically acceptable carrier(s), diluent(s) or excipient(s). This pharmaceutical composition is sometimes referred to as the amylin analogue pharmaceutical composition or the amylin analogue medicament.

15 In a preferred aspect, the combination of the invention comprises the separate administration of the amylin analogue pharmaceutical composition and the amylin analogue pharmaceutical composition to a subject.

20 **Therapeutic uses, methods and dosage regimes**

In a broad aspect, the present invention provides a GLP-1/GLP-2 dual agonist and an amylin analogue according to the invention for use as one or more medicaments.

25 In an aspect, the present invention relates to a GLP-1/GLP-2 dual agonist and an amylin analogue according to the invention for use in therapy.

In an aspect, the present invention relates to a GLP-1/GLP-2 dual agonist and an amylin analogue according to the invention for use in the treatment or prevention of a disease or disorder.

30 In preferred embodiments, the disease or disorder is obesity or obesity-related.

In one aspect, the present invention relates to a GLP-1/GLP-2 dual agonist and an amylin analogue according to the invention for use in a method of treating or
35 preventing a disease or disorder.

In an aspect, the present invention relates to a GLP-1/GLP-2 dual agonist and an amylin analogue according to the invention for use in reducing the weight of a subject.

5 The GLP-1/GLP-2 dual agonist and the amylin analogue according to the invention may be used for therapeutic or cosmetic purposes.

The invention further relates to a GLP-1/GLP-2 dual agonist and an amylin analogue for use in methods that are not directed towards treating diseases or disorders, *per se*. Such uses and methods may be considered preventative of diseases or disorders
10 in so far as they may be utilised prior to the onset of disease (e.g., pre diagnosis) e.g., to ameliorate unwanted physiological characteristics or alter certain physiological parameters. Furthermore, such uses or methods may be considered cosmetic.

It will be understood that the GLP-1/GLP-2 dual agonist and the amylin analogue for
15 use according to the invention will have utility in any of the diseases or disorders disclosed herein (e.g., in relation to each of the GLP-1/GLP-2 dual agonist and the amylin analogue).

It will be understood that the uses of a GLP-1/GLP-2 dual agonist and an amylin
20 analogue of the invention described herein may be expressed as methods. All features of the uses of the invention described herein are applicable to the corresponding methods of the invention.

Accordingly, the invention provides a method of preventing or treating a disease or
25 disorder, the method comprising administering to a subject a GLP-1/GLP-2 dual agonist and an amylin analogue. In some embodiments, the disease or disorder is obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia, diabetes, pre-diabetes, metabolic syndrome or hypertension.

30 The invention also provides a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss, the method comprising administering to a subject a GLP-1/GLP-2 dual agonist and an amylin analogue. The method may be therapeutic or non-therapeutic (i.e. cosmetic).

35 Likewise, it will be understood that the uses of a GLP-1/GLP-2 dual agonist and an amylin analogue of the invention described herein may be expressed as dosage

regimes. All features of the uses of the invention described herein are applicable to the corresponding dosage regimes of the invention.

Thus, the invention provides a dosage regime for preventing or treating a disease or disorder, the dosage regime comprising administering to a subject a GLP-1/GLP-2 dual agonist and an amylin analogue. In some embodiments, the disease or disorder is obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia, diabetes, pre-diabetes, metabolic syndrome or hypertension.

10

The invention also provides a dosage regime for reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss, the dosage regime comprising administering to a subject a GLP-1/GLP-2 dual agonist and an amylin analogue. The dosage regime may be therapeutic or non-therapeutic (i.e. cosmetic).

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 **Example 1: Effects of GLP-1/GLP-2 dual agonist alone and in combination with the Amylin Analogue in DIO Rats**

The dual GLP-1/GLP-2 agonist used in this example is the GLP-1/GLP-2 dual agonist Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-
25 isoGlu)]QAARDFIAWLIQHKITD-OH (SEQ ID NO: 5).

The amylin analogue used in this example is the amylin analogue [19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNT-Hyp-NH₂ (SEQ ID NO: 6).

30

This study was performed to assess the effect of treatment with a combination of the GLP-1/GLP-2 dual agonist and the amylin analogue in diet-induced obese (DIO) rats.

Healthy male Sprague Dawley rats were obtained from Taconic Denmark (Taconic Biosciences A/S). The rats weighed approximately 225-275g at arrival and were allowed to acclimatize 4 weeks. To generate diet-induced obese (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. Animals were housed in groups of 2, on a 12-hour light and 12-hour dark cycle (with lights on at 6:00 AM-6:00 PM) at standard temperature and humidity conditions (20-23°C; 50-80% relative humidity) with ad libitum access to domestic quality tap water.

DIO animals (n=9/group) were stratified based on bodyweight on day-3 and were treated for 4 weeks from day 0 with either vehicle (once daily (q.d.)), GLP-1/GLP-2 dual agonist (100 nmol/kg, q.d.), the amylin analogue (10 nmol/kg, every other day (q.o.d.) or the combination of GLP-1/GLP-2 dual agonist plus the amylin analogue (100 nmol/kg, q.d. and 10 nmol/kg, q.o.d., respectively).

Outcomes included cumulative food intake, body weight (BW), and fasting blood glucose levels. The food intake was measured every other day from day -2 and throughout the experiment and the cumulative food intake for each treatment group was calculated (Figure 1).

For the BW outcome animals were weighed on Day -2 (baseline weight) and every day throughout the study. The percent (%) BW change from baseline was calculated for each day from day 0 to 28 (Figure 2 A) and on day 28 (day before termination) from baseline (day 0) (Figure 2 B).

Overnight fasting blood glucose levels (mmol/L) were determined at baseline (day-1) and at termination (day 29) in overnight fasted animals. Blood samples sampled from the tail vein (10 µl) in Na-heparin-coated capillary tubes by use of the Biosen enzyme-based electrode method using a S-line Biosen glucose analyzer (EKF diagnostics, US). The measured mean fasting blood glucose levels (mmol/L) for each group at day 29 and the mean blood glucose levels for all animals at day -1 (dotted horizontal line) are shown in Figure 3. Exposure was measured in plasma for both compounds at using LC-MS/MS.

Combination therapy with the GLP-1/GLP-2 dual agonist and the amylin analogue, achieved a significant, sustained and greater cumulative reduction in food intake compared to vehicle; $p < 0.0001$ and compared to the GLP-1/GLP-2 dual agonist monotherapy; $p < 0.05$ (Figure 1) and resulted in significant, sustained and greater BW

reduction compared to vehicle and either monotherapy treatment (Figure 2 A and B). The data show: $-12.4\% \pm 0.9$ the GLP-1/GLP-2 dual agonist, $-5.9\% \pm 0.4$ the amylin analogue, $-18.9\% \pm 1.8$ combination therapy, $+4.4\% \pm 0.7$ vehicle, all changes relative to initial body weight of the DIO animals; $p < 0.0001$ for all groups vs vehicle, $p < 0.01$ for combination vs the GLP-1/GLP-2 dual agonist and $p < 0.0001$ for combination vs the amylin analogue.

The GLP-1/GLP-2 dual agonist monotherapy treatment and combination treatment resulted in significantly reduced fasting blood glucose levels compared to vehicle; $p < 0.001$ (Figure 3).

- 10 It was observed that the treatment with the GLP-1/GLP-2 dual agonist, the amylin analogue and the combination of the two were well tolerated. Exposure of the GLP-1/GLP-2 dual agonist and the amylin analogue measured in plasma showed no difference between dosing as a single compound or when dosed together as a combination of both compounds (Figure 4).
- 15 In conclusion, in the DIO rat model the GLP-1/GLP-2 dual agonist potentiated the effect of the amylin analogue monotherapy on body weight loss, suggesting additive effect of this combination therapy for the management of overweight, obesity and obesity-related comorbidities.

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

5 scope and spirit of the invention. Although the invention has been described in connection with specific preferred 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

10 are intended to be within the scope of the following aspects.

CLAIMS

1. A GLP-1/GLP-2 dual agonist and an amylin analogue for use in a method of preventing or treating a disease or disorder, wherein the GLP-1/GLP-2 dual agonist and the amylin analogue are administered to a subject.
- 5 2. A GLP-1/GLP-2 dual agonist and an amylin analogue for use according to claim 1, wherein the disease or disorder is obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnea, inadequate glucose control, glucose tolerance, dyslipidaemia, diabetes, pre-diabetes, metabolic syndrome or hypertension.
- 10 3. A GLP-1/GLP-2 dual agonist and an amylin analogue for use in a method of reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss.
- 15 4. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 3, wherein the GLP-1/GLP-2 dual agonist is Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (SEQ ID NO: 5), or a pharmaceutically acceptable salt or solvate thereof.
- 20 5. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 4, wherein the method comprises administering the GLP-1/GLP-2 dual agonist to the subject at a dose of about 0.5 mg to about 10.0 mg.
- 25 6. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 5, wherein the method comprises administering the GLP-1/GLP-2 dual agonist to the subject at a dose of about 0.5 mg to about 7.5 mg, preferably about 1.0 mg to about 7.5 mg, preferably about 1.0 to about 6.0 mg, preferably about 1.0 to about 4.0 mg, preferably about 1.0 to about 3.5 mg.
- 30 7. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 6, wherein the method comprises administering the GLP-1/GLP-2 dual agonist to the subject once a day at a dose of about 0.5 mg to about 10.0 mg per day.

35

8. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 7, wherein the method comprises administering the GLP-1/GLP-2 dual agonist to the subject once a day at a dose of about 0.5 mg to about 7.5 mg per day, preferably once a day at a dose of about 1.0 mg to about 7.5 mg per day,
5 preferably once a day at a dose of about 1.0 to about 6.0 mg per day, preferably once a day at a dose of about 1.0 to about 4.0 mg per day, preferably once a day at a dose of about 1.0 to about 3.5 mg per day.

9. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any
10 one of claims 1 – 8, wherein the amylin analogue is [19CD]-isoGlu-
RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-Hyp-NH₂
(SEQ ID NO: 6), or a pharmaceutically acceptable salt or solvate thereof.

10. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any
15 one of claims 1 – 9, wherein the method comprises administering the amylin analogue to the subject at a dose of about 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.

20
11. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 10, wherein the method comprises administering the amylin analogue to the subject every other day at a dose of about 0.5 mg to about 10.0 mg per day, preferably every other day at a dose of about 0.6 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 mg to about 7.5 mg mg per day, preferably every other day at a dose of about 1.2 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 6.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 4.0 mg mg per day, preferably every other day at a dose of about 2.4 to about 3.5 mg mg per day.

30
12. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 11, wherein the GLP-1/GLP-2 dual agonist and/or the amylin analogue, or the pharmaceutically acceptable salt or solvate thereof, are independently in admixture with a carrier, excipient, and/or vehicle.

35
13. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to claim 12, wherein the carrier is a pharmaceutically acceptable carrier.

14. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 13, wherein the amylin analogue is in a pharmaceutical composition, wherein the pharmaceutical composition comprises one or more of:
- 5 (i) at a concentration of from about 0.4 mg/ml to about 25 mg/ml of one or more amylin analogue;
- (ii) present in a solution with a buffer concentration of about 0.5 mM to 25 mM;
- (iii) present in a solution with a pH of about 5.8 to about 6.9; and/or
- (iv) the amylin analogue is provided as a chloride salt.
- 10
15. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 14, wherein the GLP-1/GLP-2 dual agonist is in a pharmaceutical composition, wherein the pharmaceutical composition comprises one or more of:
- (i) at least about 1 mg/mL of one or more GLP-1/GLP-2 dual agonist
- 15 (ii) 5 mM to about 50 mM of phosphate buffer component
- (iii) about 190 mM to about 240 mM of mannitol; and/or
- (iv) the pH is about pH 8.0.
16. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any
- 20 one of claims 1 – 15, wherein the subject is human.
17. The GLP-1/GLP-2 dual agonist and the amylin analogue for use according to any one of claims 1 – 16, wherein the GLP-1/GLP-2 dual agonist and the amylin analogue are administered by injection, preferably by subcutaneous injection.
- 25
18. A dosage regime for preventing or treating a disease or disorder, the dosage regime comprising administering to a subject a GLP-1/GLP-2 dual agonist and an amylin analogue.
- 30
19. A dosage regime for reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss, the dosage regime comprising administering to a subject a GLP-1/GLP-2 dual agonist and an amylin analogue.
20. The dosage regime according to claim 18 or claim 19 comprising the features
- 35 according to any one of claims 1 to 17.