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

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

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

SUMMARY OF THE INVENTION

In one aspect, the present disclosure refers to use of GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for preventing or treating a disease or disorder, wherein the first and second medicaments are to be administered to a subject.

In another aspect, the present disclosure refers to use of a GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss.

In a further aspect, the present disclosure refers to use of a GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in a dosage regime for preventing or treating a disease or disorder.

In yet another aspect, the present disclosure refers to use of a GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in a dosage regime for reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss.

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

In one example, there is described 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 example, the subject is a human subject.

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

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

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

In one example, 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.

In one example, 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.

The disclosure 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.

In some examples the uses or methods described herein may be considered cosmetic.

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

In one example, the disclosure refers to 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.

The present disclosure further describes the combination of a GLP-1/GLP-2 dual agonist and amylin analogue for use in therapy. In yet another example, the disclosure refers to the combination of a GLP-1/GLP-2 dual agonist and amylin analogue for use as a medicament. Also described is a combination of a GLP-1/GLP-2 dual agonist and amylin analogue for use in a method of medical treatment.

The disclosure also describes 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.

The disclosure also describes 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.

The disclosure also describes 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.

The disclosure also describes 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.

The disclosure also describes 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 example, the GLP-1/GLP-2 dual agonist and the amylin analogue are in separate medicament. In a preferred example, 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

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 example, the GLP-1/GLP-2 dual agonist medicament is in a form for suitable subcutaneous (s/c or s.c.) administration to a subject. The amylin analogue medicament may be in any form for suitable administration to a subject. In a preferred example, 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 example, the GLP-1/GLP-2 dual agonist medicament is delivered to the subject daily. In a preferred example, the GLP-1/GLP-2 dual agonist medicament is delivered to the subject once daily. In a preferred example, the amylin analogue medicament is delivered to the subject every other day. In a preferred example, the amylin analogue medicament is delivered to the subject once every other day.

For some examples, 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 examples, 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, 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 examples, 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.

For some examples, 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.

For some examples, preferably 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

(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.

For some examples, 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, preferably about 2.4 to about 4.0 mg, preferably about 2.4 to about 3.5 mg.

For some examples, 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.

For some examples, 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;

(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 examples, 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;

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 examples, 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 examples, 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:

(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:

(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.

The disclosure also refers to 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.

The disclosure also refers to 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 levels or reduced HDL/LDL ratio), diabetes (e.g. Type 2 diabetes, gestational diabetes), pre-diabetes, metabolic syndrome or hypertension.

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

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

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 disclosure have activities of both GLP-1 and GLP-2.

In one example, 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.

The disclosure also refers to a composition comprising a dual agonist as described herein, 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.

In one example, the amylin analogue is:
[19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNT-Hyp-NH_2 (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.

The disclosure also refers to a composition comprising the amylin analogue described herein, or a pharmaceutically acceptable salt or solvate thereof, together with a carrier, excipient or vehicle. The carrier may be a pharmaceutically acceptable carrier.

CLAIMS

1. Use of a GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for preventing or treating a disease or disorder, wherein the first and second medicaments are to be administered to a subject.

2. The 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.

3. Use of a GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss.

4. The 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.

5. The use according to any one of claims 1 – 4, wherein the GLP-1/GLP-2 dual agonist is to be administered to the subject at a dose of about 0.5 mg to about 10.0 mg.

6. The use according to any one of claims 1 – 5, wherein the GLP-1/GLP-2 dual agonist is to be administered 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.

7. The use according to any one of claims 1 – 6, wherein the GLP-1/GLP-2 dual agonist is to be administered to the subject once a day at a dose of about 0.5 mg to about 10.0 mg per day.

8. The use according to any one of claims 1 – 7, wherein the GLP-1/GLP-2 dual agonist is to be administered 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.

9. The use according to any one of claims 1 – 8, wherein the amylin analogue is [19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNT-Hyp-NH_2 (SEQ ID NO: 6), or a pharmaceutically acceptable salt or solvate thereof.

10. The use according to any one of claims 1 – 9, wherein the amylin analogue is to be administered 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.

11. The use according to any one of claims 1 – 10, wherein the amylin analogue is to be administered 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.

12. The 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.

13. The use according to claim 12, wherein the carrier is a pharmaceutically acceptable carrier.

14. The use according to any one of claims 1 – 13, wherein the second medicament is 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;
(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.

15. The use according to any one of claims 1 – 14, wherein the first medicament is 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
(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 use according to any one of claims 1 – 15, wherein the subject is human.

17. The use according to any one of claims 1 – 16, wherein the first medicament and the second medicament are to be administered by injection, preferably by subcutaneous injection.

18. Use of a GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in a dosage regime for preventing or treating a disease or disorder.

19. Use of a GLP-1/GLP-2 dual agonist in the manufacture of a first medicament and use of an amylin analogue in the manufacture of a second medicament, wherein the first and second medicaments are to be used in a dosage regime for reducing or inhibiting weight gain, reducing food intake, reducing appetite, or promoting weight loss.

20. The use according to claim 18 or claim 19, comprising the features according to any one of claims 1 to 17.