Claims

1. Use of a glucose-dependent insulinotropic peptide receptor (GIPR) antagonist GIP peptide consisting of the amino acid sequence SEQ ID NO:1:

3 – 4 – 5 - 6 7 8 9 10 11 12 13 14 15
X_1 – G – T - F – I – S – E – Y – S – I – Aib – X_2 – E –

16 17 18 19 20 21 22 23 24 25 26 27 28 29
K - I - K – Q – Q – E – F – V – E – W – L – L – A – Q –

30 31 32 33 34 35 36 37 38 39
K – P - S - S – G – A – P – P – P – S (SEQ ID NO:1),

wherein X_1 is E, glutaric acid, adipic acid or succinic acid; and
wherein X_2 is M, L or Nle;
or a functional variant thereof, wherein said variant comprises 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, and 25 to 39 of SEQ ID NO: 1,
wherein said GIPR antagonist GIP peptide comprises a fatty acid molecule attached, directly or via a linker, to the side chain amino group of the amino acid residue at position 18 of SEQ ID NO:1, or said functional variant thereof,
in the manufacture of a medicament for use in combinatorial therapy for treating obesity, an obesity-related disorder and/or dyslipidemia, wherein said medicament is to be administered in combination with a glucagon-like peptide-1 (GLP-1) receptor agonist.

2. Use of a GIPR antagonist GIP peptide consisting of the amino acid sequence SEQ ID NO:1:

3 – 4 – 5 - 6 7 8 9 10 11 12 13 14 15
X_1 – G – T - F – I – S – E – Y – S – I – Aib – X_2 – E –

16 17 18 19 20 21 22 23 24 25 26 27 28 29
K – I - K – Q – Q – E – F – V – E – W – L – L – A – Q –

30 31 32 33 34 35 36 37 38 39
K – P - S - S – G – A – P – P – P – S (SEQ ID NO:1),

wherein X_1 is E, glutaric acid, adipic acid or succinic acid; and

wherein X_2 is M, L or Nle;

or a functional variant thereof, wherein said variant has 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, and 25 to 39 of SEQ ID NO: 1,

wherein said GIPR antagonist GIP peptide comprises a fatty acid molecule attached, directly or via a linker, to the side chain amino group of the amino acid residue at position 18 of SEQ ID NO:1, or said functional variant thereof,

in the manufacture of a medicament for use in combinatorial therapy for inhibiting or reducing one or more of i) food intake, ii) body weight, iii) fasting blood levels of glucose, iv) fasting blood levels of insulin, v) insulin resistance, vi) fasting blood levels of triglycerides, vii) fasting blood levels of cholesterol and viii) fasting blood levels of low-density lipoprotein (LDL) cholesterol,

wherein said medicament is to be administered in combination with a GLP-1 receptor agonist.

3. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein said GLP-1 receptor agonist is a GLP-1 peptide, such as a protease-resistant analogue of hGLP-1.

4. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein said GLP-1 receptor agonist is selected from the group consisting of exenatide (SEQ ID NO:22), Lixisenatide (SEQ ID NO:23), albiglutide (SEQ ID NO:24), liraglutide (SEQ ID NO:25), taspoglutide (SEQ ID NO:26), dulaglutide (SEQ ID NO:27), semaglutide

(SEQ ID NO:19), efpeglenatide, exendin-4 (Ex4; SEQ ID NO:22), Ex4(1-30) (SEQ ID NO:29), Ex4(9-39) (SEQ ID NO:30), Ex(9-30) (SEQ ID NO:28), hGLP-1(1-37) (SEQ ID NO:32), hGLP-1(7-36) (SEQ ID NO:33), hGLP-1(7-37) (SEQ ID NO:34), hGLP-1(1-36) (SEQ ID NO:35), hGLP-1(9-36) (SEQ ID NO:36), A7-hGLP-1(7-36) (SEQ ID NO:37) and A10-hGLP-1(7-36) (SEQ ID NO:28), or a functional variant thereof.

5. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein said GLP-1 receptor agonist is:
i. hGLP-1(7-37), or a variant thereof, such as a variant having one or two individual amino acid substitutions, and optionally comprising a fatty acid molecule:
ii. (Arg34)hGLP-1(7-37) (SEQ ID NO:25), or a variant thereof, such as variant having one amino acid substitution, and optionally comprising a fatty acid molecule;
iii. (Arg34)hGLP-1(7-37) (SEQ ID NO:25) comprising a fatty acid molecule attached to the lysine at position 26 of said (SEQ ID NO:25), or a variant thereof, such as a variant having one amino acid substitution;
iv. (Arg34)hGLP-1(7-37) (SEQ ID NO:25) comprising a fatty acid molecule attached to the lysine at position 26;
v. (Aib8)(Arg34)hGLP-1(7-37) (SEQ ID NO:19), comprising a fatty acid molecule attached to the lysine at position 26;
vi. liraglutide; or
vii. semaglutide.

6. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein said GLP-1 receptor agonist is semaglutide.

7. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein said GLP-1 peptide is a liquid formulation of semaglutide, or a solid oral dosage form composition of semaglutide.

8. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein said GLP-1 receptor agonist is a non-peptide GLP-1 receptor agonist, or a small molecule GLP-1 receptor agonist.

9. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein said GLP-1 receptor agonist is a GLP-1 receptor activating antibody, a dual or triple acting GLP-1 receptor agonist, or a GLP-1/glucagon dual receptor agonist.

10. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein

i. X_1 of SEQ ID NO:1 is E or glutaric acid;
ii. X_2 of SEQ ID NO:1 is L or Nle;
iii. X_1 of SEQ ID NO:1 is E and X_2 of SEQ ID NO:1 is L;
iv. X_1 of SEQ ID NO:1 is glutaric acid and X_2 of SEQ ID NO:1 is L; or
v. X_1 of SEQ ID NO:1 is glutaric acid and X_2 of SEQ ID NO:1 is Nle.

11. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein the GIPR antagonist GIP peptide is selected from:
EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:6;
GIP(3-30) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
EGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:7;
GIP(3-30) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],
EGTFISEYSIALEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:8;
GIP(3-30) [D9E;M14L;D15E;H18K;D21E;N24E],
EGTFISEYSIANleEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:9;
GIP(3-30) [D9E;M14Nle;D15E;H18K;D21E;N24E],
XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:11;
GIP(3-30) [E3Glutaric acid(X);D9E;A13Aib;
M14L;D15E;H18K;D21E;N24E],
XGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:12;
GIP(3-30) [E3Glutaric acid(X);D9E;A13Aib;
M14Nle;D15E;H18K;D21E;N24E],
XGTFISEYSIALEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:13;
GIP(3-30) [E3Glutaric acid(X);D9E; M14L;D15E;H18K;D21E;N24E],
XGTFISEYSIAibMEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:14;
GIP(3-30) [E3Glutaric acid(X);D9E;A13Aib;D15E;H18K;D21E;N24E],

EGTFISEYSIAibMEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:15; GIP(3-30)[D9E;A13Aib;D15E;H18K;D21E;N24E], EGTFISEYSIAMEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:16; GIP(3-30) [D9E;D15E;H18K;D21E;N24E], XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:20; GIP(3-30) [E3Succinic acid(X);D9E;A13Aib; M14L;D15E;H18K;D21E;N24E], and XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS; SEQ ID NO:21; GIP(3-30) [E3Adipic acid(X);D9E;A13Aib; M14L;D15E;H18K;D21E;N24E], or a functional variant thereof comprising 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, and 25 to 39 of said GIPR antagonist GIP peptide.

12. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein the GIPR antagonist GIP peptide is C-terminally carboxylated (-COOH).

13. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein the fatty acid molecule is a straight-chain fatty acid or a branched fatty acid; and/or wherein the fatty acid molecule is a diacyl fatty acid molecule; and/or
wherein said fatty acid molecule comprises an acyl group of the formula $CH_3(CH_2)_nCO$-, wherein n is in an integer of 4 to 24; and/or wherein said fatty acid molecule comprises an acyl group of the formula $COOH(CH_2)_nCO$- (dicarboxylic acid), wherein n is an integer of 4 to 24; and/or
wherein said fatty acid molecule comprises an acyl group selected from $COOH(CH_2)_{14}CO$-, $COOH(CH_2)_{16}CO$-, $COOH(CH_2)1_8CO$- and $COOH(CH_2)_{20}CO$-.

14. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims,
wherein said fatty acid molecule is attached via a linker, and wherein said linker comprises one or more moieties individually selected from:
a. α-amino acid, γ-amino acid and ω-amino acid,

b. one or more amino acids selected from succinic acid, Lys, Glu and Asp,
c. one or more amino acids selected from Gly and Ser,
d. one or more amino acids selected from Ala, Glu, Lys and Leu,
e. one or more of γ-aminobutanoyl (γ-aminobutyric acid), γ-Glu (γ-glutamic acid), β-Asp (β-asparagyl), β-Ala (β-alanyl), 2-aminoisobutyric acid (Aib) and Gly, and
f. [8-amino-3,6-dioxaoctanoic acid]n (AEEAcn), wherein n is an integer of 1 to 50, such as an integer of 1 to 4, 1 to 3, or 1 to 2.

15. The use of the GIPR antagonist GIP peptide according to any of the preceding claims, wherein said fatty acid molecule is attached, directly or via a linker, to the side chain amino group of a lysine residue at position 18 of SEQ ID NO:1, or said variant of SEQ ID NO:1; or wherein said fatty acid molecule is attached to the side chain amino group of an ornithine residue at position 18 of a variant of SEQ ID NO:1 substituted with an ornithine residue at position 18.

16. The use of the GIPR antagonist GIP peptide according to any one of the preceding claims, wherein the GIPR antagonist GIP peptide is selected from

EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:6; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:6; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
EGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:7; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],
EGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:7; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],
EGTFISEYSIALEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:8; GIP(3-30)+Cex(31-39) [D9E;M14L;D15E;H18K;D21E;N24E],

EGTFISEYSIANleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:9; GIP(3-30)+Cex(31-39) [D9E;M14Nle;D15E;H18K;D21EN24E], XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:11; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib; M14L;D15E;H18K;D21E;N24E], XGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:12; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib; M14Nle;D15E;H18K;D21E;N24E], XGTFISEYSIALEKIKQQEFVEWLLAQKPSSGAPPPS-OH-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:13; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E; M14L;D15E;H18K;D21E;N24E], XGTFISEYSIAibMEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:14; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib;D15E;H18K;D21E;N24E], EGTFISEYSIAibMEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:15; GIP(3-30)+Cex(31-39) [D9E;A13Aib;D15E;H18K;D21E;N24E], EGTFISEYSIAMEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:16; GIP(3-30)+Cex(31-39) [D9E;D15E;H18K;D21E;N24E], XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:11; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:6; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:11; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-(GGGS-C16-diacid/18K); SEQ ID NO:6; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-(ALEA-C16-diacid/18K); SEQ ID NO:6; GIP(3-30)+Cex(31-39)

[D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], XGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K); SEQ ID NO:12; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E], EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-(Aib-C16-diacid/18K); SEQ ID NO:6; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-(KAAAEKAAAEKAAAE-C16-diacid/18K); SEQ ID NO:6; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:20; GIP(3-30)+Cex(31-39) [E3Succinic acid(X);D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], and XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:21; GIP(3-30)+Cex(31-39) [E3Adipic acid(X);D9E;A13Aib; M14L;D15E;H18K;D21E;N24E],
or a functional variant thereof comprising 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, and 25 to 39 of said GIPR antagonist GIP peptide.

17. A composition comprising, separately or together, or a kit of parts comprising, a GIPR antagonist GIP peptide and a GLP-1 receptor agonist, wherein said GIPR antagonist GIP peptide consists of the amino acid sequence SEQ ID NO:1:

3 – 4 – 5 - 6 7 8 9 10 11 12 13 14 15
X_1 – G – T - F – I – S – E – Y – S – I – Aib – X_2 – E –

16 17 18 19 20 21 22 23 24 25 26 27 28 29
K – I - K – Q – Q – E – F – V – E – W – L – L – A – Q –

30 31 32 33 34 35 36 37 38 39
K – P - S - S – G – A – P – P – P – S (SEQ ID NO:1),

wherein X_1 is E, glutaric acid, adipic acid or succinic acid; and
wherein X_2 is M, L or Nle;

or a functional variant thereof, wherein said variant comprises 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, and 25 to 39 of SEQ ID NO: 1,
wherein said GIPR antagonist GIP peptide comprises a fatty acid molecule attached, directly or via a linker, to the side chain amino group of the amino acid residue at position 18 of SEQ ID NO:1, or said functional variant thereof.

18. Use of a composition or kit of parts according to claim 17 in the manufacture of a medicament for treatment of obesity, an obesity-related disorder and/or dyslipidemia; and/or in the manufacture of a medicament for inhibiting or reducing one or more of i) food intake, ii) body weight, iii) fasting blood levels of glucose, iv) fasting blood levels of insulin, v) insulin resistance, vi) fasting blood levels of triglycerides, vii) fasting blood levels of cholesterol and viii) fasting blood levels of low-density lipoprotein (LDL).

19. The use of the GIPR antagonist GIP peptide according to any one of claims 1 to 16 or the use of the composition according to any one of claims 17 and 16, wherein said obesity-related disorder is selected from a heart disease, stroke, high blood pressure, high blood cholesterol, high blood low-density lipoprotein (LDL) cholesterol, high blood triglycerides, dyslipidemia, gallbladder disease and gallstones, NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis), osteoarthritis, gout, breathing problems such as sleep apnea and asthma, insulin resistance, diabetes mellitus, and binge eating.

20. The use of the GIPR antagonist GIP peptide according to any one of claims 1 to 16 and 19, the composition according to claim 17, or the use of the composition according to any one of claims 18 and 19, wherein said GIPR antagonist GIP peptide is selected from:
EGTFIS**E**YSI**AibLE**KI**K**QQ**E**FV**E**WLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:6; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], or a functional variant thereof comprising 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, 25 to 39 of SEQ ID

NO:6;

XGTFIS**E**YSI**AibLE**KI**K**QQ**E**FV**E**WLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:11; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib;M14L;D15E;H18K;D21E;N24E], or a functional variant thereof comprising 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, 25 to 39 of SEQ ID NO: 11;

and

XGTFIS**E**YSI**AibNleE**KI**K**QQ**E**FV**E**WLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-diacid/18K; SEQ ID NO:12; GIP(3-30)+Cex(31-39) [E3Glutaric acid(X);D9E;A13Aib; M14Nle;D15E;H18K;D21E;N24E], or a functional variant thereof comprising 1, 2 or 3 individual amino acid substitutions at any one of positions 4 to 8, 10 to 13, 16, 17, 19, 20, 22, 23, 25 to 39 of SEQ ID NO: 12;

and wherein said GLP-1 receptor agonist is semaglutide.