acute effects of GLP-1 and GIP on insulin secretion, the incretins have some long-term effects. Evidence from several laboratories shows that GLP-1 receptor agonists protect pancreatic β-cells by inhibiting apoptosis and enhancing proliferation. For instance, a study by Farilla *et al.* showed that GLP-1 has anti-apoptotic effects in human islets (Farilla, L, Endocrinology 144: 5149-58 (2003)). Such effects have not been reported for GIP until recently. Weidenmaier *et al.* reported that a DPP-4 resistant GIP analogue had anti-apoptotic effects (Weidenmaier, SD, PLOS One 5(3): e9590 (2010)). Interestingly, in mouse models of diabetes and obesity, the combination of the GLP-1 receptor agonist Liraglutide and GIP showed superior glucose-lowering and insulinotropic effects compared to treatment with Liraglutide and GIP alone (Gault, VA, Clinical Science 121: 107–117 (2011)).

[0004] Chronic treatment with GLP-1 receptor agonists causes significant weight loss in diabetic humans. Interestingly, extended use of DPP-4 inhibitors in similar patients does not consistently change body weight. Evidence suggests (Matthias Tschöp oral presentation at ADA (American Diabetes Association), 2011) that body weight loss associated with GLP-1 agonist treatment is enhanced when GLP-1 and GIP are co-administered. In rodents, co-administration of GLP-1 and GIP results in greater body weight loss than GLP-1 treatment alone. Thus, in addition to improving blood glucose control, GIP may also enhance GLP-1-mediated body weight loss.

Summary ~~of the Invention~~

[0005] Broadly, the present ~~invention~~ disclosure concerns truncated GIP analogues which comprise one or more substitutions as compared to wild-type GIP and which may have the property of an altered, preferably increased GLP-1 activity, e.g., as assessed in *in vitro* efficacy assays. In the present ~~invention~~ disclosure it has been found that GIP-GLP1 dual acting receptor agonists are superior to existing and marketed GLP-1 analogues because the dual agonists offer improved glycemic control,and enhanced body weight loss. The GIP-GLP1 dual agonists (also known as GIP analogues) may thus be used as therapeutics for type 2 diabetes mellitus, obesity and related disorders.

[0006] More particularly, preferred GIP analogues of the present disclosure ~~invention~~ comprise non-conservative substitutions at one or more of amino acid positions 1, 2, 3, 7, 9, 13, 14, 15, 17, 19, 20, 21, 22, 23, 24, 27, 28, 29, and 30 of the wild-type

GIP sequence in combination with Ile,Gln, Lys, Arg or Glu in position 17, optionally in combination with further conservative or non-conservative substitutions at one or more of amino acid positions 10,11, and 16; and acylation of one or more of amino acid positions 15, 16, 17, 19, 20, 24, 27, 28 and 30 and/or a substitution or deletion of one or more of amino acids corresponding to positions 30 to 42 of the wild-type GIP sequence.

[0007] In some embodiments, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula I:

R^1- X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I) (SEQ ID NO 59)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is: His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp, Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X17 is Ile, Lys, Gln, Arg or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys or Arg;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Glu, Lys, Gly or Tyr;

X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0008] In an aspect~~some embodiments~~, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula I':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I') (SEQ ID NO 61)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr, Ser or Ile;
X9 is Asp or Glu;
X10 is Tyr, Leu or Ser;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Met, Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Gly, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Lys, Gly or Ala;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;

X34 is Asn, Gly, Ala, Lys or absent;

X35 is Asp, Ala, Pro, Glu or absent;

X36 is Trp, Pro, Lys or absent;

X37 is Lys, Pro, Glu or absent;

X38 is His, Pro, Ser, Lys or absent;

X39 is Asn, Ser or absent;

X40 is Ile or absent;

X41 is Thr or absent;

X42 is Gln or absent; and

R^2 is $-NH_2$ or $-OH$;
and wherein said analogue has agonist activity at the GIP and GLP-1 receptors.

[0009] In other embodiments, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula I(a):

R^1- X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(a)) (SEQ ID NO 33)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X17 is Ile, Lys, Gln, Arg or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys or Arg;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu ;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Glu, Lys or Tyr;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;

X34 is Asn, Gly, Ala, Lys or absent;

X35 is Asp, Ala, Pro, Glu or absent;

X36 is Trp, Pro, Lys or absent;

X37 is Lys, Pro, Glu or absent;

X38 is His, Pro, Ser, Lys or absent;

X39 is Asn, Ser or absent;

X40 is Ile or absent;

X41 is Thr or absent;

X42 is Gln or absent; and

R^2 is $-NH_2$ or -OH.

[0010] In other embodiments, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula I(a)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(a)') (SEQ ID NO 62)

or a pharmaceutically acceptable salt or solvate thereof,

X42 is Gln or absent; and

R^2 is $-NH_2$ or -OH.

[0011] In other embodiments, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula I(b):

R^1- X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)) (SEQ ID NO 1)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr or Ser;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X17 is Ile, Lys, Gln, Arg or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys or Arg;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu ;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys or Ser;

X28 is Ala or Aib;

X29 is Gln, Gly, Aib or Tyr;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0012] In other embodiments, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula I(b)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)') (SEQ ID NO 63)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr or Ser;
X9 is Asp or Glu;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;
X21 is Asp, Ala or Glu;
X23 is Val, Ile or Leu;
X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Glu, Val or Ile;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Gly, Aib or Ala;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0013] In some embodiments, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula II:

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II)
(SEQ ID NO 60)
wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr, Leu or Ser
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X14 is Leu;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X17 is Ile or Lys;

X19 is Gln, Lys, Ala or Glu;

X20 is Lys or Arg;

X21 is Ala or Glu;

X23 is Val or Ile;

X24 is Asn or Glu;

X27 is Leu, Glu, Ser, Lys or Val;

X28 is Aib, Ala, Ser or Arg;

X29 is Aib, Glu, Gly or Lys;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

[0014] In another aspect~~some embodiments~~, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula II':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-X12-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II')

(SEQ ID NO 64)

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Aib or Gly;

X7 is Thr, Ile or Ser;

X10 is Tyr or Leu;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X15 is Asp or Glu;

X16 is Ser, Glu or Lys;

X19 is Gln or Ala;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;

X28 is Aib, Ala, Ser or Arg;

X29 is Gln, Aib, Ala, Gly or Lys;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH;

and wherein said analogue has agonist activity at the GIP and GLP-1 receptors.

[0015] In other embodiments, a GIP analogue of the ~~invention~~ present disclosure is represented by the general Formula II(a):

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a))

(SEQ ID NO 34)

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Aib or Gly;

X7 is Thr, Ile or Ser;

X10 is Tyr, Leu or Ser

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Leu;

X15 is Asp or Glu;

X16 is Ser, Glu or Lys;

X17 is Ile or Lys;

X19 is Gln, Lys, Ala or Glu;

X20 is Lys or Arg;

X21 is Ala or Glu;

X23 is Val or Ile;

X24 is Asn or Glu;

X27 is Leu, Glu, Ser, Lys or Val;

X28 is Aib, Ala, Ser or Arg;

X29 is Aib, Glu or Lys;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

[0016] In other embodiments, a GIP analogue of the present disclosure ~~invention~~ is represented by the general Formula II(a)':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a)')

(SEQ ID NO 65)

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Aib or Gly;

X7 is Thr, Ile or Ser;

X10 is Tyr or Leu;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X15 is Asp or Glu;

X16 is Ser, Glu or Lys;

X19 is Gln, Lys, Ala or Glu;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;

X28 is Aib, Ala, Ser or Arg;

X29 is Gln, Aib, Ala, or Gly;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

[0017] In other embodiments, a GIP analogue of the present disclosure ~~invention~~ is represented by the general Formula II(b):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-X14-X15-Lys-X17-Ala-Gln-X20-X21-Phe-X23-X24-Trp-Leu-X27-Ala- X29-X30-Y1-R^2 (II(b))

(SEQ ID NO 2)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala, Tyr or Aib;

X14 is Leu;

X15 is Asp or Glu;

X17 is Ile or Lys;

X20 is Lys or Arg;

X21 is Ala or Glu;

X23 is Val or Ile;

X24 is Asn or Glu;

X27 is Leu or Val;

X29 is Aib or Gly;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is -NH_2 or -OH.

[0018] In other embodiments, a GIP analogue of the present disclosure ~~invention~~ is represented by the general Formula II(b)':

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-X23-Glu-Trp-Leu-X27-X28- Ala-X30-Y1-R^2 (II(b)')

(SEQ ID NO: 66)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala or Tyr;

X15 is Asp or Glu;

X16 is Lys or Ser;

X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X27 is Leu, Glu or Val;
X28 is Arg or Ser;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

[0019] In other embodiments, a GIP analogue of the present disclosure ~~invention~~ is represented by the general Formula II(c):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-Val-X24-Trp-Leu-X27-Ala- X29-X30-Y1-R^2 (II(c))
(SEQ ID NO: 67)
or a pharmaceutically acceptable salt or solvate thereof,
wherein
R^1 is Hy-, Ac or pGlu;
X7 is Thr or Ser;
X13 is Aib or Tyr ;
X15 is Asp or Glu;
X16 is Glu, Lys or Ser;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X24 is Glu or Asn
X27 is Leu, Glu or Val;
X29 is Gln or Aib;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

[0020] In other embodiments, a GIP analogue of the present disclosure ~~invention~~ is represented by the general Formula II(d):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-Ala-Phe-Val-Glu-Trp-Leu-X27-Ala-Gln-X30-Y1-R^2 (II(d))

(SEQ ID NO: 68)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Aib or Tyr;

X15 is Asp or Glu;

X16 is Glu, Lys or Ser;

X20 is Lys, His or Arg;

X27 is Leu, Glu or Val;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is -NH_2 or -OH.

In another aspect, there is provided a GIP analogue selected from:

Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2,

pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS-NH_2; and
Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS-NH_2; and
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

In another aspect, there is provided a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed herein for use in a therapeutic method.

In another aspect, there is provided a pharmaceutical composition comprising a GIP analogue as disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier.

In another aspect, there is provided the use of a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed herein for the preparation of a medicament for the treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

In another aspect, there is provided the use of a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed herein for the preparation of a medicament for the treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

In another aspect, there is provided a therapeutic kit comprising a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed herein, optionally in combination with a pharmaceutically acceptable carrier.

In another aspect, there is provided a device comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23, for delivery of the GIP analogue to a subject.

[0021] Without wishing to be bound by any particular theory, the Isoleucine at position 7 of native GIP appears to provide significant selectivity for the GIP receptor. A small polar residue (e.g. Thr or Ser) at position 7 may increase potency and/or selectivity at the GLP-1 receptor.

[0022] Without wishing to be bound by any particular theory, it is believed that substitution of Met found in position 14 of native GIP with a hydrophobic residue like leucine is important for enhancing GLP-1 receptor activity and so increase potency and/or selectivity at the GLP-1 receptor. The substitution of Met at position 14 with leucine also reduces the potential for oxidation, so increasing the chemical stability of the compounds. The non-conservative and non-obvious substitution of Ile for Lys in position 17 may enhance GLP-1 receptor activity and in addition provide a handle for acylation to prolong half life of the peptide.

[0023] Without wishing to be bound by any particular theory, the histidine at position 18 of native GIP appears to provide significant selectivity for the GIP receptor. A non-conservative substitution of histidine in position 18 with a small

hydrophobic residue (e.g. Ala) may increase potency and/or selectivity at the GLP-1 receptor.

[0024] Without wishing to be bound by any particular theory, it is believed that a truncation of the C-terminal of native GIP may be performed without affecting the GIP receptor activity. The truncation can be of any length (1-13 amino acids) down to a 29 amino acid GIP peptide.

[0025] Without wishing to be bound by any particular theory, the addition of Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser or Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser at or after position 29 or at or after position 30 of a native GIP or a GIP analogue may increase GLP1 receptor activity.

[0026] Aib in amino acid position 2 may render GIP peptide having from 42 amino acids down to 29 amino acids resistant to DPP-IV cleavage.

[0027] Aib in amino acid position 13 and/or 29 will enhance the stability of the peptide towards enzymatic degradation. In addition, without wishing to be bound by any particular theory, the Aib mayenhance the helicity of the peptide and hence enhance the GLP-1 receptor activity. Furthermore, Nal1 in position 22 may also render the peptide stable to enzymatic degradation.

[0028] In a preferred embodiment, the GIP analogue of the ~~invention~~ present disclosure comprises:

Glu at position 24 and/or Ala at position 21, truncated or full length, which may be combined with any of the following:

Thr at position 7, Leu at position 14, truncated or full length;

Thr at position 7, Leu at position 14, Ala at position 18, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, (Aib at position 13 and/or 29), truncated or full length;

Thr at position 7, Leu at position 14, Ala at position 19, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, (Aib at position 13 and/or 29), truncated or full length;

Thr at position 7, Leu at position 14, Gln at position 19, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, Gln at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Gln at position 19, truncated or full length; or

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Gln at position 19, (Aib at position 13 and/or 29), truncated or full length.

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, Leu at position 27, Ser at position 28 and Ala at position 29, truncated or full length; or

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, Glu at position 27, Ser at position 28 and Ala at position 29, truncated or full length.

[0029] Some embodiments of the ~~invention~~ present disclosure are:

1. A GIP analogue represented by the general Formula I:

R^1-X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42-R^2 (I) (SEQ ID NO 59)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X36 is Trp, Pro, Lys or absent;

X37 is Lys, Pro, Glu or absent;

X38 is His, Pro, Ser, Lys or absent;

X39 is Asn, Ser or absent;

X40 is Ile or absent;

X41 is Thr or absent;

X42 is Gln or absent; and

R^2 is $-NH_2$ or $-OH$;
and wherein said analogue has agonist activity at the GIP and GLP-1 receptors.

2. The GIP analogue of claim 1, wherein the GIP analogue is represented by the general Formula I(b)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)') (SEQ ID NO 63)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr or Ser;

X9 is Asp or Glu;

X10 is Tyr or Leu;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X14 is Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Ser or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Glu, Val or Ile;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Gly, Aib or Ala;

X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

3. A GIP analogue represented by the general Formula II':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-X12-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II')

(SEQ ID NO 64)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X17 is Ile or Lys;
X19 is Gln or Ala;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;

X28 is Aib, Ala, Ser or Arg;

X29 is Gln, Aib, Ala, Gly or Lys;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or $-OH$;

and wherein said analogue has agonist activity at the GIP and GLP-1 receptors.

4. The GIP analogue or pharmaceutically acceptable salt or solvate of claim 43, wherein the GIP analogue is represented by the general Formula II(a)':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a)')

(SEQ ID NO 65)

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Aib or Gly;

X7 is Thr, Ile or Ser;

X10 is Tyr or Leu;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X15 is Asp or Glu;

X16 is Ser, Glu or Lys;

X19 is Gln, Lys, Ala or Glu;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;

X28 is Aib, Ala, Ser or Arg;

X29 is Gln, Aib, Ala or Gly;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

8. A GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDKKAQRAFVEWLLAQ (SEQ ID NO: 70).

9. A GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA (SEQ ID NO: 71).

10. A GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 5 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDEKAAKEFIEWLESA (SEQ ID NO: 72).

11. A GIP analogue ~~compound~~ or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 7 wherein X24 is Glu and/or X21 is Ala.

12. A GIP analogue ~~compound~~ or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X7 is Thr and X14 is Leu.

13. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X7 is Thr, X14 is Leu and X18 is Ala.

14. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr and X14 is Leu.

15. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu and X13 and/or X29 is Aib.

16. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu and X24 is Glu,

17. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu and X29 is Gln.

18. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X21 is Ala, X24 is Glu and X29 is Gln.

19. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu, X27 is Leu and X28 is Ser.

20. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu, X27 is Glu and X28 is Ser.

21. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X20 is His, X24 is Glu, X27 is Leu and X28 is Ser.

22. A GIP analogue selected from:

Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2,

pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2;

23. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of the preceding claims with a lipophilic substituent conjugated to one or more of positions 15, 16, 17, 19, 20, 24, 27, 28 and 30.

24. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of the preceding claims for use in a therapeutic method.

25. A pharmaceutical composition comprising a GIP analogue of any one of the preceding claims, or a pharmaceutically acceptable salt~~,~~ or solvate ~~or derivative~~ thereof, in admixture with a carrier.

26. The pharmaceutical composition of claim 25, wherein the GIP analogue is a pharmaceutically acceptable acid addition salt.

27. The pharmaceutical composition of claim 25 or claim 26, which is formulated as a liquid suitable for administration by injection or infusion, or which is formulated to cause slow release of said GIP analogue.

~~28. Use of a GIP analogue of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of metabolic diseases.~~

~~29~~28. Use of a GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

~~30~~29. Use of a GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

~~31. The use of claim 30, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.~~

32. The use of claim 30, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and proinflammatory state, or a combination thereof.

33. The use of claim 32, wherein the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, and plaque buildup in artery walls, or a combination thereof.

34. The use of claim 32, wherein the prothrombotic state is selected from high fibrinogen levels in the blood and high plasminogen activator inhibitor-1 levels in the blood.

35. The use of claim 32, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.

36. The use of claim 30, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea, or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.

37. A nucleic acid molecule comprising a nucleic acid sequence encoding a GIP analogue of any one of claims 1 to 23.

38. An expression vector comprising the nucleic acid sequence of claim 37, in combination with control sequences to direct its expression.

39. A host cell transformed with the expression vector of claim 36.

40. A method of producing the GIP analogue of any one of claims 1 to 23, the method comprising culturing the host cells of claim 39 under conditions suitable for expressing the GIP analogue and purifying the GIP analogue thus produced.

~~41. A nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39 for use in therapy.~~

~~42. Use of a nucleic acid molecule according to claim 37, an expression vector according to claim 38 or a host cell according to claim 39, in the preparation of a medicament for the treatment and/or prevention of a metabolic disorder.~~

~~43. The use of claim 42, wherein the metabolic disorder is selected from diabetes and obesity.~~

~~44. A method of treating a stomach and/or bowel-related disorder in a patient in need thereof by administering an effective amount a GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39.~~

~~45. A method of treatment and/or prevention of a metabolic disease or disorder in a patient in need thereof comprising administering to said patient an effective amount of the GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39.~~

~~46. The method of claim 45, wherein the metabolic disease or disorder is selected from diabetes and obesity.~~

~~47~~30. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23 for use in a method of treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof~~in a patient in need thereof comprising the step of administering to said patient an effective amount of the GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39~~.

~~48~~31. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23 for use in a method of treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea~~in a patient in need thereof comprising the step of administering to said patient an effective amount of the GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39~~.

~~49. The method of claim 47, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.~~

~~50. The method of claim 47, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.~~

~~51. The method of claim 50, wherein the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, plaque buildup in artery walls, or a combination thereof.~~

~~52. The method of claim 50, wherein the prothrombotic state is selected from high fibrinogen levels in the blood and high plasminogen activator inhibitor-1 levels in the blood.~~

~~53. The method of claim 50, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.~~

~~54. The method of claim 48, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.~~

~~55~~32. A therapeutic kit comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23, ~~a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39, each~~ optionally in combination with a pharmaceutically acceptable carrier.

~~56~~33. A device comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23, ~~a nucleic acid molecule according to claim 37, an expression vector according~~

~~to claim 38, or a host cell according to claim 39,~~ for delivery of the GIP analogue to a subject.

~~57. A pharmaceutical composition comprising the GIP analogue of any one of claims 1 to 23 for use in treating a stomach and bowel-related disorder in a patient in need thereof.~~

~~58. A pharmaceutical composition comprising the GIP analogue of any one of claims 1 to 23 for use in treatment and/or prevention of a metabolic disease or disorder in a patient in need thereof.~~

~~59. The pharmaceutical composition of claim 58, wherein the metabolic disorder is selected from diabetes and obesity.~~

~~60~~34. A pharmaceutical composition comprising ~~the~~ a GIP analogue or pharmaceutically acceptable salt or solvate according to~~of~~ any one of claims 1 to 23 for use in treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof~~in a patient in need thereof~~.

~~61~~35. A pharmaceutical composition comprising ~~the~~ a GIP analogue or pharmaceutically acceptable salt or solvate according to~~of~~ any one of claims 1 to 23 for use in treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea~~in a patient in need thereof~~.

~~62. The pharmaceutical composition of claim 60, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.~~

~~63. The pharmaceutical composition of claim 60, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.~~

~~64. The pharmaceutical composition of claim 63, wherein the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, plaque buildup in artery walls, or a combination thereof.~~

~~65. The pharmaceutical composition of claim 63, wherein the prothrombotic state is selected from high fibrinogen levels in the blood, and high plasminogen activator inhibitor-1 levels in the blood.~~

~~66. The pharmaceutical composition of claim 63, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.~~

~~67. The pharmaceutical composition of claim 61, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease, and obesity induced sleep apnea.~~