

human amylin. Thus, the numbering of any given residue in Formula I above, and in other formulae elsewhere in this specification, reflects the corresponding residue in human amylin when optimally aligned therewith and does not necessarily reflect its linear position in the particular sequence.

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(It will be apparent that any of the relevant formulae presented in this specification could be written to include residues X21-X22 at the appropriate positions, wherein X21 and X22 are absent.)

- 10 It has surprisingly been found that simultaneous deletion of the residues at positions X21 and X22 (and even additionally at positions X19 and X20) leads to active and stable amylin analogues. Further, without wishing to be bound by any particular theory, it is believed that the deletion of these residues may enhance the chemical stability of the molecules, especially at neutral and/or alkaline pH. Fibrillation and precipitation of the
15 compounds may also be reduced. Thus the compounds may have superior properties for formulation as compared to existing amylin analogues.

Furthermore, the compounds described here show similar or even increased activity compared to wild type amylin (e.g. agonist activity at the hAMYR3 and/or hAMYR1 and/or
20 hCTR2 receptors), despite being methylated at the same positions as IAPP-GI (which has lower activity than wild type amylin).

In some examples of formula I it may be desirable that:

X31 is Glu;

- 25 X19-X20 is Ser-Ser or is absent; and/or

X37 is Hyp or Pro.

It may be desirable that the amylin analogue contains at least one of His14, Asn14, Aad14, Gln17 and Thr17.

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If X14 is Asp, then it may be desirable that X17 is Asn, Gln, Glu, Thr or Aad.

X17 is Gln may be particularly preferred.

In some circumstances, it may be desirable that X35 is not a hydrophobic residue, e.g. Phe. Such residues may increase tendency towards fibrillation in some formulations.

Z may be an amino acid sequence of formula II:

5 Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-Glu-Val-Gly-Ser-X35-Thr-X37 (II);

wherein

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

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

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

X17 is selected from the group consisting of His, Asn, Gln, Glu, Lys and Aad;

X19-X20 is Ser-Ser or is absent;

X35 is selected from the group consisting of Asp, Glu, Asn, Ser, Orn, Aad, Gly and Thr;
and

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

and wherein the compound has at least one residue selected from:

X3 is Gln;

X14 is His or Aad;

X17 is Asn, Gln, Glu or Aad; and

20 X35 is Ser, Phe, Orn, Aad, Gly or Thr.

In some examples of formula II, X17 may be selected from His and Gln.

Z may be an amino acid sequence of formula III:

25 Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-Glu-Val-Gly-Ser-X35-Thr-X37 (III);

wherein

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

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

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

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

X19-X20 is Ser-Ser or is absent;

X35 is selected from the group consisting of Asp, Glu, Asn, Aad and Gly; and

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

and wherein the compound has at least one residue selected from:

X3 is Gln;

X14 is His or Aad;

X17 is Gln; and

10 X35 is Aad.

In any of the formulae described above, it may be desirable that:

X10 is selected from Gln and Glu;

and/or

15 X35 is selected from Asp, Glu, Asn and Aad, e.g. X35 is selected from Asp and Asn.

Additionally or alternatively, it may be that X3 is selected from Asn and Gly and/or X17 is Gln. The presence of Gln at position X17 is believed to correlate with good levels of chemical and physical stability.

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Additionally or alternatively, X35 is Asn and/or X37 is Hyp.

In some examples of the formulae described above:

X3 is Gln;

25 X10 is selected from Glu and Asp;

X14 is selected from His and Aad;

X35 is selected from Gly and Asn; and

X37 is selected from Pro and Hyp.

In other examples of the formulae described above:

X3 is Gly;

5 X10 is selected from Glu and Asp;

X14 is selected from His and Aad;

X35 is selected from Gly and Asn; and

X37 is selected from Pro and Hyp.

10 Combinations of specific residues which may be present in any of the amylin analogues described include:

Gly3 + Glu10;

Asn3 + Glu10;

Gln3 + Glu10;

15 Asn3 + Gln10; or

Gln3 + Asp10.

In some examples, X14 is selected from His and Aad, and/or X17 is Gln.

20 For example, the combination of Aad14 and Gln17 appears to provide good activity.

Additionally or alternatively, X17 may be Gln, X31 may be Glu and X37 may be Hyp, i.e. the analogue may contain the combination Gln17 + Glu31 + Hyp37.

In some examples, X19-X20 is Ser-Ser. In other examples X19-X20 is absent.

Certain residue combinations which may be favourable for chemical stability include:

X3 is Gly, X10 is Glu and X14 is His;

X3 is selected from Asn and Gln, X10 is Glu and X14 is His;

5 X3 is Gly, X10 is Glu and X14 is selected from Aad and Asp;

X10 is Asp and X14 is Aad;

X14 is selected from Aad and His, X31 is Glu and X37 is selected from Pro and Hyp; and
X14 is Aad, X31 is Glu and X37 is Hyp.

10 Of these combinations, the following may additionally (or alternatively) have a favourable effect on activity:

X3 is Gly, X10 is Glu and X14 is selected from Aad and Asp;

X14 is selected from Aad and His, X31 is Glu and X37 is selected from Pro and Hyp;

X14 is Aad, X31 is Glu and X37 is Hyp.

15

For example, the compound may comprise the residues:

Gly3 + Glu10 + His14

Asn3 + Glu10 + His14;

Gln3 + Glu10 + His14;

20 Gly3 + Glu10 + Aad14;

Gly3 + Glu10 + Asp14;

Asp10 + Aad14;

His14 + Glu31 + Pro37

His14 + Glu31 + Hyp37

25 Aad14 + Glu31 + Pro37; and

Aad14 + Glu31 + Hyp37.

Yet further combinations of desirable residues include:

Gly3 + Glu31;

30 Gly3 + Ser19 + Ser20 + Glu31

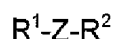
Gly3 + Glu10 + Glu31 + Asn35 + Hyp37; and

Gly3 + Glu10 + Ser19 + Ser20 + Glu31 + Asn35 + Hyp37.

Any of the above-described residues and combinations of residues may be combined

35 except where inconsistent with one another.

In another aspect, the invention also provides an amylin analogue which is a compound having the formula:



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

Z is an amino acid sequence selected from the group consisting of:

RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP;

- 10 RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr; and
RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr;
or a pharmaceutically acceptable salt or solvate thereof.

Thus, the amylin analogue may have the formula:

- 15 R^1-Z-R^2

wherein

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

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

- 20 Z is an amino acid sequence selected from the group consisting of:

RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsNT-Hyp

RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsNT-Hyp

- 25 RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsNT-Hyp

RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsST-Hyp

RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsFT-Hyp

In some examples, R¹ is M or M-L-, and/or R² is NH₂.

Specific amylin analogues of the invention include:

- [19CD]-isoGlu-RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- 5 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂
- 10 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-T-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-T-Hyp-NH₂
- 15 [19CD]-isoGlu-RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-T-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-T-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-T-Hyp-NH₂
- 20 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVG-S-Orn-T-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVG-S-Aad-T-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-T-Hyp-NH₂
- 25 [19CD]-isoGlu-RCNTATCATQRLAHFLHRF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂

[19CD]-isoGlu-R-C()-QTAT-C()-ATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂ (Compd. 92)

[19CD]-isoGlu-R-C()-QTAT-C()-ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂ (Compd. 93)

5 [19CD]-isoGlu-R-C()-QTAT-C()-ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP-NH₂ (Compd. 94)

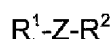
[19CD]-isoGlu-R-C()-QTAT-C()-ATDRLA-Aad-FLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂ (Compd. 95)

10 [19CD]-isoGlu-R-C()-QTAT-C()-ATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂ (Compd. 96)

wherein [19CD] represents [19-carboxynonadecanoyl];

and pharmaceutically acceptable salts and solvates thereof.

15 In certain examples, the amylin analogue of the invention is not a compound having the formula:



wherein

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

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

Z is an amino acid sequence selected from the group consisting of:

RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

25 RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr

RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr

RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp

RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp

RCGTATCATERLAHFLELSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp

- RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Aad-T-Hyp
 5 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCNTATCATQRLAHFLHRF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 and
 RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 10 or a pharmaceutically acceptable salt or solvate thereof.

For example, in such examples, the compound is not:

- [19CD]-isoGlu-RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
 15 [19CD]-isoGlu-RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
 [19CD]-isoGlu-RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂
 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂
 20 [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
 [19CD]-isoGlu-RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
 25 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-Hyp-NH₂
 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp-NH₂
 30 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Aad-T-Hyp-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂

[19CD]-isoGlu-RCNTATCATQRLAHFLHRF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂

or

- 5 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂;
(wherein [19CD] represents [19-carboxynonadecanoyl])

and pharmaceutically acceptable salts and solvates thereof;

or any such compounds comprising an intramolecular disulphide bridge formed between the cysteine residues present at positions 2 and 7 of the amino acid sequence.

- 10 In another aspect, the invention further provides a composition comprising an amylin analogue as described above. The composition may be a pharmaceutical composition, and may comprise a pharmaceutically acceptable carrier, excipient or vehicle.

- In another aspect, there is provided a device comprising an amylin analogue as described herein, for delivery of the amylin analogue to a subject, optionally further comprising an anti-diabetic agent, an anti-obesity agent, an agent for treatment of metabolic syndrome, an anti-dyslipidemia agent, an anti-hypertensive agent, a proton pump inhibitor, or an anti-inflammatory agent.
- 15

- The disclosure further provides a method for the synthesis of an amylin analogue as described above. The method may comprise the steps of synthesising the peptide by solid-phase or liquid-phase methodology, and optionally isolating and/or purifying the final product. The method may further comprise the step of forming a disulphide bond between the thiol groups of the cysteine side chains at positions 2 and 7.
- 20

In another aspect, the present invention further provides an amylin analogue of the invention for use in a method of medical treatment.

- 25 The amylin analogues are useful, inter alia, in the reduction of food intake, promotion of weight loss, and inhibition or reduction of weight gain. As a result, they may be used for treatment of a variety of conditions, diseases, or disorders in a subject, including, but not limited to, obesity and various obesity-related conditions, diseases, or disorders, such as diabetes (e.g. type 2 diabetes), hypertension, dyslipidemia, sleep apnea and cardiovascular disease. The subject may be affected by obesity accompanied by at least one weight-related co-morbid condition, such as diabetes (e.g. type 2 diabetes), hypertension, dyslipidemia, sleep apnea and cardiovascular disease. It will be understood that the amylin analogues may thus be administered to subjects affected by conditions characterised by inadequate control of appetite or otherwise over-feeding, such as binge-
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eating disorder and Prader-Willi syndrome. It will be clear that the analogues can be used for treatment of combinations of the conditions described.

Thus, the disclosure provides an amylin analogue of the invention for use in a method of treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess
5 body weight. Treatment may be achieved, for example, by control of appetite, feeding, food intake, calorie intake and/or energy expenditure.

The disclosure also provides an amylin analogue of the invention for use 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,
10 obesity-linked gallbladder disease and obesity-induced sleep apnea and respiratory problems, degeneration of cartilage, osteoarthritis, and reproductive health complications of obesity or overweight such as infertility. The subject may be affected by obesity accompanied by at least one weight-related co-morbid condition, such as diabetes (e.g. type 2 diabetes), hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

15 The disclosure also provides an amylin analogue of the invention for use 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 with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, hypertension, atherogenic dyslipidemia, hepatic
20 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 (including diabetic cardiomyopathy and heart failure as a diabetic complication) coronary heart disease, peripheral artery disease or stroke, and combinations thereof.

25 The disclosure also provides an amylin analogue of the invention for use in a method of lowering circulating LDL levels and/or increasing HDL/LDL ratio.

Effects of amylin analogues on these conditions may be mediated in whole or in part via an effect on body weight, or may be independent thereof.

30 In another aspect, the invention further provides use of an amylin analogue of the invention in the manufacture of a medicament for treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess body weight.

In another aspect, the invention also provides use of an amylin analogue of the invention in the manufacture of a medicament for 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 obesity or overweight such as infertility. The subject may be affected by obesity accompanied by at least one weight-related co-morbid condition, such as diabetes (e.g. type 2 diabetes), hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

10 In another aspect, the invention also provides use of an amylin analogue of the invention in the manufacture of a medicament for the 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 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 (including diabetic cardiomyopathy and heart failure as a diabetic complication) coronary heart disease, peripheral artery disease or stroke, and combinations thereof.

In another aspect, the invention also provides use of an amylin analogue of the invention in the manufacture of a medicament for lowering circulating LDL levels and/or increasing HDL/LDL ratio.

25 The disclosure further provides a method of treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess body weight in a subject, comprising administering a therapeutically effective amount of an amylin analogue of the invention to the subject.

30 The disclosure also provides 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 obesity or overweight such as infertility in a subject, comprising administering a therapeutically effective amount of an amylin analogue of the invention to the subject. The subject may be affected by obesity

accompanied by at least one weight-related co-morbid condition, such as diabetes (e.g. type 2 diabetes), hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

The disclosure also provides a method of prevention or treatment of Alzheimer's disease, diabetes, type 1 diabetes, type 2 diabetes, pre-diabetes, insulin resistance syndrome,
5 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), macrovascular disease, microvascular
10 disease, diabetic heart (including diabetic cardiomyopathy and heart failure as a diabetic complication) coronary heart disease, peripheral artery disease or stroke, and combinations thereof, in a subject, comprising administering a therapeutically effective amount of an amylin analogue of the invention to the subject.

The disclosure further provides a method of lowering circulating LDL levels and/or
15 increasing HDL/LDL ratio in a subject, comprising administering a therapeutically effective amount of an amylin analogue of the invention to the subject.

The disclosure further provides the use of an amylin analogue as described above in a method of cosmetic (i.e. non-therapeutic) weight loss. It will be understood that references to therapeutic uses of amylin analogues and methods comprising
20 administration of amylin analogues may equally be taken to encompass uses and administration of such compositions.

Further aspects and embodiments of the present invention will become apparent from the disclosure below.

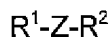
DETAILED DESCRIPTION OF THE INVENTION

25 Unless otherwise defined herein, scientific and technical terms used herein shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature employed herein in connection with techniques of chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, is that well known and commonly used in
30 the art.

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

CLAIMS

1. An amylin analogue which is a compound having the formula:



5 wherein

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

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

Z is an amino acid sequence of formula I:

10 Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-X31-Val-Gly-Ser-X35-Thr-X37 (I);

wherein

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

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

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

X17 is selected from the group consisting of His, Asn, Gln, Glu, Thr, Val, Lys and Aad;

X19-X20 is selected from the group consisting of Ser-Ser, Val-Val, Ser-Val and Val-Ser, or is absent;

X31 is selected from the group consisting of Asp, Glu and Asn;

20 X35 is selected from the group consisting of Asp, Glu, Asn, Ser, Phe, Orn, Aad, Gly and Thr; and

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

and wherein the compound has at least one residue selected from:

X3 is Gln;

25 X14 is His, Asn or Aad;

X17 is Asn, Gln, Glu, Thr or Aad;

X19-X20 is Val-Ser or Ser-Val; and

X35 is Ser, Phe, Orn, Aad, Gly or Thr;

5 or a pharmaceutically acceptable salt or solvate thereof; wherein said amylin analogue has agonist activity at one or more of hAMYR1, hAMYR2 and hAMYR3.

2. An amylin analogue according to claim 1 wherein:

(a) X31 is Glu;

(b) X19-X20 is Ser-Ser or is absent; and/or

10 (c) X37 is Hyp or Pro.

3. An amylin analogue according to claim 1 wherein Z is an amino acid sequence of formula II:

15 Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-Glu-Val-Gly-Ser-X35-Thr-X37 (II);

wherein

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

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

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

20 X17 is selected from the group consisting of His, Asn, Gln, Glu, Lys and Aad;

X19-X20 is Ser-Ser or is absent;

X35 is selected from the group consisting of Asp, Glu, Asn, Ser, Orn, Aad, Gly and Thr;
and

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

25 and wherein the compound has at least one residue selected from:

X3 is Gln;

X14 is His or Aad;

X17 is Asn, Gln, Glu or Aad; and

X35 is Ser, Phe, Orn, Aad, Gly or Thr.

5

4. An amylin analogue according to any one of the preceding claims wherein X17 is selected from His and Gln.

5. An amylin analogue according to claim 1 wherein Z is an amino acid sequence of
10 formula III:

Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-
Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-Glu-Val-Gly-Ser-X35-Thr-X37 (III);

wherein

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

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

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

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

X19-X20 is Ser-Ser or is absent;

X35 is selected from the group consisting of Asp, Glu, Asn, Aad and Gly; and

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

and wherein the compound has at least one residue selected from:

X3 is Gln;

X14 is His or Aad;

X17 is Gln; and

X35 is Aad.

6. An amylin analogue according to any one of the preceding claims wherein:

(i) X10 is selected from Gln and Glu;

5 and/or

X35 is selected from Asp, Glu, Asn and Aad;

(ii) X3 is selected from Asn and Gly, and/or X17 is Gln; and/or

(iv) X35 is Asn and/or X37 is Hyp.

10 7. An amylin analogue according to any one of claims 1 to 5 wherein:

X3 is Gln;

X10 is selected from Glu and Asp;

X14 is selected from His and Aad;

X35 is selected from Gly and Asn; and

15 X37 is selected from Pro and Hyp.

8. An amylin analogue according to any one of the preceding claims:

(i) comprising the residues:

X3 is Gly;

20 X10 is selected from Glu and Asp;

X14 is selected from His and Aad;

X35 is selected from Gly and Asn; and

X37 is selected from Pro and Hyp;

(ii) comprising the residues:

Gly3 + Glu10;

Asn3 + Glu10;

Gln3 + Glu10;

5 Asn3 + Gln10; or

Gln3 + Asp10;

(iii) wherein X14 is selected from His and Aad, and/or X17 is Gln

(iv) comprising the residues:

Gln17 + Glu31 + Hyp37

10 Gly3 + Glu10 + His14

Asn3 + Glu10 + His14;

Gln3 + Glu10 + His14;

Gly3 + Glu10 + Aad14;

Gly3 + Glu10 + Asp14;

15 Asp10 + Aad14;

His14 + Glu31 + Pro37

His14 + Glu31 + Hyp37

Aad14 + Glu31 + Pro37;

Aad14 + Glu31 + Hyp37;

20 Gly3 + Glu31; or

Gly3 + Glu10 + Glu31 + Asn35 + Hyp37; and/or

(v) wherein X19-X20 is Ser-Ser, optionally comprising the residues:

Gly3 + Ser19 + Ser20 + Glu31 or

Gly3 + Glu10 + Ser19 + Ser20 + Glu31 + Asn35 + Hyp37.

25

9. An amylin analogue according to any one of the preceding claims wherein Z is:

RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-Hyp

RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp
 RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-T-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-T-Hyp
 5 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVG-S-Orn-T-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVG-S-Aad-T-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSG-T-Hyp
 RCNTATCATQRLAHFLHRF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 10 RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 RCGTATCATERLANFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp
 RCGTATCATERLAHFLKRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp
 RCNTATCATQRLAHFLHRVSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 15 RCNTATCATQRLAHFLHRVSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCPTATCATDRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSDTP
 RCNTATCATQRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSNTP
 20 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSDTP
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-T-Hyp
 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-T-Hyp
 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-T-Hyp
 25 RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-T-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-T-Hyp
 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-T-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP

RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP
 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP
 RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP
 5 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP
 RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp
 RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp
 10 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Apr
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-TP
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 15 RCNTATCATQRLAHFL-Aad-RSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Aad-T-Hyp
 RCGTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 20 RCGTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 RCQTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 RCPTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSNT-Hyp
 25 RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSDT-Hyp
 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNTP
 RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNTP
 RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 RCPTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp

RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 RCNTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 RCPTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 RCNTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp
 5 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
 10 RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSAad-T-Hyp
 RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSAad-T-Hyp
 RCGTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 15 RCNTATCATQRLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTTP
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
 20 RCNTATCATQRLAHFLERSSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP
 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP
 RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp
 RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp
 25 RCQTATCATDRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp
 RCQTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 RCQTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP

RCQTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP

RCQTATCATDRLA-Aad-FLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-Hyp or

RCQTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP

- 5 10. An amylin analogue which is a compound having the formula:

R^1-Z-R^2

wherein

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

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

Z is an amino acid sequence selected from the group consisting of:

RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP;

RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr; and

RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr;

- 15 or a pharmaceutically acceptable salt or solvate thereof.

11. An amylin analogue according to any one of the preceding claims wherein R^1 is M- or M-L-.

- 20 12. An amylin analogue according to claim 11, wherein M is an alkanoyl group, optionally wherein M is selected from 15-carboxy-pentadecanoyl, 17-carboxy-heptadecanoyl and 19-carboxy-nonadecanoyl.

- 25 13. An amylin analogue according to any one of the preceding claims wherein R^1 is M-L- and L is a residue of an amino acid selected from the group consisting 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, 4-aminobutanoyl, 5-aminopentanoyl, 6-aminohexanoyl, 7-aminoheptanoyl, 8-aminooctanoyl, 9-aminononanoyl, 10-aminodecanoyl and 8Ado. e.g. wherein L is a γ -Glu residue.

30

14. An amylin analogue according to any one of the preceding claims wherein R² is NH₂.
15. An amylin analogue according to claim 1 which is selected from the group consisting of:
 - [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
 - [19CD]-isoGlu-RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
 - [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
 - 10 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
 - [19CD]-isoGlu-RCGTATCATERLAHFLRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
 - [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSP-Hyp-NH₂
 - 15 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSP-Hyp-NH₂
 - [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSP-T-Hyp-NH₂
 - [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSP-T-Hyp-NH₂
 - 20 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSP-T-Hyp-NH₂
 - [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSP-Hyp-NH₂
 - [19CD]-isoGlu-RCNTATCATQRLAHFLHRF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
 - [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
 - 25 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
 - [19CD]-isoGlu-RCGTATCATERLANFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂

- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLKRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- 5 [19CD]-isoGlu-RCNTATCATQRLAHFLHRVSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLHRVSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCPTATCATDRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSSTP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- 10 [19CD]-isoGlu-RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSSTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSSTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- 15 [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- 20 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- 25 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP-NH₂

5 [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP-NH₂

[19CD]-isoGlu-RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂

[19CD]-isoGlu-RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp-NH₂

[19CD]-isoGlu-RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂

10 [19CD]-isoGlu-RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Apr-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂

15 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-TP-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂

[19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂

20 [19CD]-isoGlu-RCNTATCATQRLAHFL-Aad-RSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂

25 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Aad-T-Hyp-NH₂

- [19CD]-isoGlu-RCGTATCATERLAADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- 5 [19CD]-isoGlu-RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- [19CD]-isoGlu-RCQTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- 10 [19CD]-isoGlu-RCPTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSNH₂-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSDH₂-Hyp-NH₂
- 15 [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- [19CD]-isoGlu-RCPTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- 20 [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCNTATCATERLAADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCPTATCATERLAADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCNTATCATERLAADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH₂-Hyp-NH₂
- 25 [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH₂-Hyp-NH₂

- [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- 5 [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂
- 10 [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSAad-T-Hyp-NH₂
- [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSAad-T-Hyp-NH₂
- 15 [19CD]-isoGlu-RCGTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP-NH₂
- 20 [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTTP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP-NH₂
- 25 [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂

[19CD]-isoGlu-RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂

[19CD]-isoGlu-RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂

5 [19CD]-isoGlu-RCQTATCATDRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂

[19CD]-isoGlu-RCQTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂

10 [19CD]-isoGlu-RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂

[19CD]-isoGlu-RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂

[19CD]-isoGlu-RCQTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂

15 [19CD]-isoGlu-RCQTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP-NH₂

[19CD]-isoGlu-RCQTATCATDRLA-Aad-FLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂

[19CD]-isoGlu-RCQTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂

wherein [19CD] represents [19-carboxynonadecanoyl];

20 and pharmaceutically acceptable salts and solvates thereof.

16. An amylin analogue according to claim 10 which is selected from the group consisting of:

[19CD]-isoGlu-RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂;

25 [19CD]-isoGlu-RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂; and

[19CD]-isoGlu-RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂.

17. An amylin analogue according to any one of the preceding claims, comprising an intramolecular disulphide bridge formed between the cysteine residues present at positions 2 and 7 of the amino acid sequence.

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18. A pharmaceutical composition comprising an amylin analogue according to any one of the preceding claims, in combination with a pharmaceutically acceptable carrier, excipient or vehicle.

10 19. A device comprising an amylin analogue according to any one of claims 1 to 17, for delivery of the amylin analogue to a subject, optionally further comprising an anti-diabetic agent, an anti-obesity agent, an agent for treatment of metabolic syndrome, an anti-dyslipidemia agent, an anti-hypertensive agent, a proton pump inhibitor, or an anti-inflammatory agent.

15

20. An amylin analogue according to any one of claims 1 to 17 for use in a method of medical treatment.

20 21. Use of an amylin analogue according to any one of claims 1 to 17 in the preparation of a medicament:

(a) for treating, inhibiting or reducing weight gain, promoting weight loss, reducing food intake, and/or reducing excess body weight;

25 (b) for treating obesity, morbid obesity, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease, obesity-induced sleep apnea and respiratory problems, degeneration of cartilage, osteoarthritis, or reproductive health complications of obesity or overweight such as infertility;

30 (c) for 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 with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, hypertension, atherogenic dyslipidemia, hepatic steatosis ("fatty liver"), kidney failure, arteriosclerosis (e.g. atherosclerosis), macrovascular disease, microvascular disease, diabetic heart (including diabetic cardiomyopathy and heart failure as a diabetic complication) coronary heart disease, peripheral artery disease or stroke, and combinations thereof; or

(d) for lowering circulating LDL levels and/or increasing HDL/LDL ratio.

22. Use according to claim 21 wherein said obesity is accompanied by at least one weight-related co-morbid condition, such as diabetes (e.g. type 2 diabetes), hypertension,
5 dyslipidemia, sleep apnea and cardiovascular disease.

23. Use according to claim 21 or claim 22 wherein said amylin analogue is for administration in conjunction with an anti-diabetic agent, an anti-obesity agent, an agent for treatment of metabolic syndrome, an anti-dyslipidemia agent, an anti-hypertensive
10 agent, a proton pump inhibitor, or an anti-inflammatory agent.

24. Use according to claim 23 wherein:

(a) said anti-diabetic agent is metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, a GLP-1 receptor agonist, an SGLT2 inhibitor, a GPR40 agonist, an insulin, or
15 an insulin analogue;

(b) said anti-obesity agent is peptide YY or an analogue thereof, neuropeptide Y (NPY) or an analogue thereof, a cannabinoid receptor 1 antagonist, a lipase inhibitor, Human prolslet Peptide (HIP), a melanocortin receptor 4 agonist, a GLP-1 receptor agonist, OrlistatTM, SibutramineTM, phentermine, a melanin concentrating hormone receptor 1
20 antagonist, CCK, amylin, pramlintide or leptin;

(c) said anti-hypertension agent is an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, a diuretic, a beta-blocker or a calcium channel blocker;

(d) said anti-dyslipidemia agent is a statin, a fibrate, a niacin, a PSCK9 (Proprotein convertase subtilisin/kexin type 9) inhibitor or a cholesterol absorption inhibitor;

25 (e) said proton pump inhibitor is an agent of the benzimidazole derivative type or of the imidazopyridine derivative type; or

(f) said anti-inflammatory agent is a steroid or corticosteroid, non-steroidal anti-inflammatory agent (NSAID), a COX II inhibitor, 5-aminosalicylic acid or metformin.