

PETRELINTIDE FOR REDUCING WEIGHT WHILST PRESERVING LEAN MASS**FIELD OF THE INVENTION**

The present invention relates to the use of petrelintide to reduce body fat or inhibit gain of
5 body fat whilst preserving lean mass.

BACKGROUND TO THE INVENTION

Obesity is a currently a significant public health issue across much of the developed world
and is correlated with the development of several serious conditions, such as cardiovascular
10 disease, type 2 diabetes, sleep apnoea, and certain cancers. The standard treatment for
obesity is lifestyle intervention, including the reduction of energy intake and the increase of
exercise. However, while such interventions can achieve temporary success, it is often
challenging for patients to sustain such lifestyle changes over a long period such that the
weight loss achieved is permanent.

15 Amylin is one of a family of peptide hormones that includes amylin, calcitonin, calcitonin
gene-related peptide, adrenomedullin and intermedin (intermedin also being known as AFP-
6), and has been implicated in various metabolic diseases and disorders. Human amylin was
first isolated, purified and characterized as the major component of amyloid deposits in the
20 islets of pancreases from type 2 diabetes patients.

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

Hy-KC()NTATC()ATQRLANFLVHSSNNFGAILSSTNVGSNTY-NH₂
(SEQ ID NO: 2)

25 wherein Hy- at the N-terminus designates a hydrogen atom, corresponding to the presence
of a free amino group on the N-terminal amino acid residue [i.e. the lysine (K) residue at
sequence position number 1 in the sequence shown above], wherein -NH₂ at the C-terminus
indicates that the C-terminal carboxyl group is in the amide form, and wherein the
parentheses “()” associated with the two cysteine (C, Cys) residues at sequence positions 2
30 and 7 indicate the presence of an intramolecular disulphide bridge between the two Cys
residues.

Amylin may be beneficial in treating metabolic disorders such as diabetes and/or obesity.
Amylin is believed to regulate gastric emptying, and to suppress glucagon secretion and
35 food intake, thereby regulating the rate of glucose release to the circulation. Amylin appears
to complement the actions of insulin. Compared to healthy adults, type 1 diabetes patients

have no circulating amylin, and type 2 diabetes patients exhibit reduced postprandial amylin concentrations.

WO 2018/046719 describes amylin analogues having, inter alia, a lactam bridge instead of a
5 disulphide bridge, N-methylated residues, and a deletion corresponding to the residues
Asn21 and Asn22 of native human amylin. Such analogues have considerably lower
tendency towards fibrillation than native amylin, while also having higher potency than other
known amylin analogues.

10 SUMMARY OF THE INVENTION

Broadly, the present invention relates to methods for reducing body fat whilst preserving lean
mass in a subject. More specifically, the invention is based on the surprising finding that
administration to a subject of a long-acting amylin analogue comprising a lactam bridge
(petrelintide, compound 35) results in loss of body fat without loss of lean mass.

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The methods and uses of the invention therefore advantageously promote healthy weight
loss because when losing weight it is preferable that body fat is lost rather than lean mass
such as e.g. muscle.

20 The methods and uses of the invention may thus be useful for therapy, allowing treatment or
prevention of conditions characterised by, or associated with, excess body fat, such as
overweight, obesity and morbid obesity whilst avoiding side-effects associated with
concomitant loss of lean mass. Furthermore, petrelintide is of use particularly in treatment of
diseases associated with excess body fat and loss of lean mass (e.g. muscle wasting) as
25 excess body fat may be reduced without exacerbating loss of lean mass.

Additionally, reduction of body fat whilst retaining lean mass is often desired for cosmetic
reasons, even in subjects that do not suffer from a medical condition or disease such as
obesity. Thus, the invention also provides use of petrelintide in non-therapeutic methods of
30 reducing body fat whilst preserving lean mass.

Petrelintide is a long-acting amylin analogue comprising a lactam bridge between the amino
acids at positions 2 and 7.

35 In this respect, native amylin is known to form fibrils in aqueous solution almost instantly.
The tendency for fibrillation can be reduced by incorporating N-methylated residues (as
mentioned above) and/or by substitution of certain amino acids at various positions. Native

amylin, and the vast majority of amylin analogues (such as pramlintide) contain a disulphide bridge between cysteine residues at positions 2 and 7. The internal cyclisation which this bridge provides appears to be required for full potency and activity. Compounds containing an internal disulphide bond are frequently less chemically stable than might be desired, and
5 the presence of the bond may contribute to dimerisation and oligomerisation, e.g. via disulphide exchange reactions.

However, lactam-based cyclisations are very compatible with amylin analogues having deletions at positions 21 and 22, as the replacement of the disulphide bridge by a lactam
10 bridge leads to a substantial increase of stability in aqueous solution while other beneficial properties of these amylin analogues, such as low tendency for fibrillation, high activity and good solubility are retained.

Thus, petrelintide retains amylin receptor agonist activity (i.e. activity at the hCT-R, hAMYR1,
15 hAMYR2 and/or hAMYR3 receptors) but additionally has excellent chemical stability and resistance to fibrillation, especially but not exclusively in the neutral pH range. This enhanced chemical stability in aqueous solution would facilitate development of a corresponding pharmaceutical product, potentially even in the form of a ready-to-use formulation, e.g. at or around the neutral pH range (pH 7 – 7.4).

20 Furthermore, petrelintide is a “long-acting” amylin analogue in that it has a much longer half-life than native amylin and other “short-acting” amylin analogues. In particular, native amylin has a half-life of about 15 minutes in humans, and the amylin analogue pramlintide has a half-life of about 50 minutes in humans. In contrast, petrelintide has a half-life of about 10
25 days in humans. It may not be expected that long-acting petrelintide works in the same way as short-acting amylin receptor agonists, such as native amylin. The longer half-life of petrelintide facilitates longer dosing intervals, such as once weekly dosing.

It has now been surprisingly shown that petrelintide causes loss of body fat whilst preserving
30 lean mass, such as muscle, when administered to a subject.

Thus, it is now recognised for the first time that petrelintide combines the characteristics of potent amylin receptor agonist activity, the ability to reduce body fat whilst preserving lean mass, excellent chemical stability and resistance to fibrillation, and long half-life. In
35 particular, it may not be expected that petrelintide, as a long-acting amylin analogue, would reduce body fat whilst preserving lean mass.

The invention therefore provides a method of reducing body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

- 5 The invention also provides a method of treating or preventing overweight, obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.
- 10 The invention accordingly also provides medical uses of petrelintide or a pharmaceutically acceptable salt or solvate thereof in the methods described herein.

The amylin analogue is petrelintide, which has the following formula:

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

- 15 Hyp-NH₂ (SEQ ID NO: 1) wherein

[19CD]-isoGlu is a 19-carboxynonadecanoyl group covalently attached to the alpha amino group of an iso-glutamic acid linker;

an intramolecular lactam bridge is formed between the side chains of residues indicated by parentheses "()";

- 20 Aad refers to 2-aminoadipic acid;
Gly(Me) refers to N-methylglycine;
Ile(Me) refers to N-methylisoleucine; and
Hyp refers to 4-hydroxyproline.

- 25 Petrelintide is also referred to as Compound 35 herein.

- In some embodiments, the subject suffers from a disease associated with weight gain and loss of muscle mass. In some embodiments, the subject suffers from a disease selected from sarcopenic obesity, Duchenne muscular dystrophy (DMD), Charcot-Marie-Tooth
- 30 disease (CMT), chronic obstructive pulmonary disease (COPD), McArdle disease, hypothyroidism, testosterone deficiency syndrome (TD), heart failure and anaemia.

BRIEF DESCRIPTION OF THE FIGURES

- In the Figures, "Q2D" means administration once every 2 days, "Q4D" means administration
- 35 once every 4 days and "BID" means administration twice every day.

Figure 1 shows the actual (A) and relative (B) body weight change (day 1 = 100%) recorded on a daily basis for obese rats administered vehicle, petrelintide or liraglutide, as indicated. Data are expressed as mean $\pm$ standard error of the mean (SEM) (n = 10); treatment groups were compared to the vehicle-treated group by use of a two-way ANOVA RM followed by Bonferroni's multiple comparison tests. $\rightarrow$ indicate Q4D dosing days. *P<0.05, **P<0.01, ***P<0.001.

Figure 2 shows the relative body weight change (day 1 = 100%) recorded on day 30 for obese rats administered vehicle, petrelintide or liraglutide, as indicated. Data are expressed as mean $\pm$ standard error of the mean (SEM) (n = 10).

Figure 3 shows whole body fat composition in grams (g) (A) and whole body fat composition as percentage of body weight (%) (B) at the end of the study (day 29), and the difference in whole body fat composition (%) compared to the start of the study (terminal-baseline) (C). Data are expressed as mean $\pm$ SEM (n = 10). Treatment groups were compared to the vehicle-treated group by use of a one-way ANOVA with Dunnett's post-hoc test. (*p<0.05, ***p<0.001 v vs. Vehicle).

Figure 4 shows whole body lean mass composition in grams (g) (A) and whole body lean mass composition as percentage of body weight (%) (B) at the end of the study (day 29), and the difference in whole body lean mass composition (%) compared to the start of the study (terminal-baseline) (C). Data are expressed as mean $\pm$ SEM (n = 10). Treatment groups were compared to the vehicle-treated group by use of a one-way ANOVA with Dunnett's post-hoc test. **p<0.01, ***p<0.001 vs. vehicle.

Figure 5 shows the actual (A) and relative (B) body weight change (day 1 = 0%) recorded on a daily basis over the 21-day study period for diet-induced obese (DIO) rats administered vehicle or petrelintide, as indicated. Data is expressed as mean $\pm$ standard error of the mean (SEM) (n = 10).

Figure 6 shows mass of inguinal fat (A) and epididymal fat (B) at the end of the study (day 21) for diet-induced obese (DIO) rats administered vehicle or petrelintide, as indicated. Data is expressed as mean $\pm$ standard error of the mean (SEM) (n = 10).

Figure 7 shows mass of gastrocnemius muscle (A), soleus muscle (B), tibialis muscle (C), and extensor digitorum longus muscle (D) at the end of the study (day 21) for diet-induced

obese (DIO) rats administered vehicle or petrelintide, as indicated. Data is expressed as mean $\pm$ standard error of the mean (SEM) (n = 10).

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

General definitions

20 Unless specified otherwise, the following definitions are provided for specific terms used in the present written description. All other terms will be understood as having a meaning that is common in the art as would be attributed to them by the person skilled in the art.

Throughout this specification, the word “comprise”, and grammatical variants thereof, such
25 as “comprises” or “comprising”, will be understood to imply the inclusion of a stated integer or component, or group of integers or components, but not the exclusion of any other integer or component, or group of integers or components.

The singular forms “a,” “an,” and “the” include the plurals unless the context clearly dictates
30 otherwise.

The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” may be used interchangeably.

35 Throughout the present description and claims, in representing agonist peptides the conventional three-letter and one-letter codes for naturally occurring amino acids are used, i.e.:

A (Ala), G (Gly), L (Leu), I (Ile), V (Val), F (Phe), W (Trp), S (Ser), T (Thr), Y (Tyr), N (Asn), Q (Gln), D (Asp), E (Glu), K (Lys), R (Arg), H (His), M (Met), C (Cys) and P (Pro);

as well as generally accepted three-letter codes for other α -amino acids, such as 2-aminoadipic acid (e.g. (2S)-2-aminoadipic acid [also known as (2S)-2-aminohexanedioic

5 acid]) ("Aad"),

4-hydroxyproline, also referred to herein as hydroxyproline (e.g. (2S,4R)-4-hydroxyproline [also denoted (4R)-4-hydroxy-L-proline]) ("Hyp" or "4Hyp"),

N-methylglycine (also known as sarcosine (Sar)) ("Gly(Me)"), and

N-methylisoleucine ("Ile(Me)").

10

Such other α -amino acids may be shown between hyphens "-" (e.g. "-Aad-") when used in a general formula or sequence in the present specification, especially when the rest of the formula or sequence is shown using the single letter code.

15 Unless otherwise specified, amino acid residues in peptides of the invention are of the L-configuration. However, D-configuration amino acids may be incorporated. In the present context, an amino acid code written with a small letter represents the D-configuration of said amino acid, e.g. "k" represents the D-configuration of lysine (K).

20 Among sequences disclosed herein are sequences incorporating a "Hy-" or "H-" moiety at the amino terminus (N-terminus) of the sequence, and either an "-OH" moiety or an "-NH₂" moiety at the carboxy terminus (C-terminus) of the sequence. In such cases, and unless otherwise indicated, a "Hy-" or "H-" moiety at the N-terminus of the sequence in question indicates a hydrogen atom, corresponding to the presence of a free primary or secondary
25 amino group at the N-terminus. An "-OH" moiety at the C-terminus of the sequence indicates a hydroxy group, corresponding to the presence of a carboxy (COOH) group at the C-terminus. An "-NH₂" moiety at the C-terminus of the sequence indicates an amino group [e.g. R² = NH₂ in the general formulas], corresponding to the presence of an amido (CONH₂) group at the C-terminus. In each sequence, a C-terminal "-OH" moiety may be substituted
30 for a C-terminal "-NH₂" moiety, and vice-versa.

Parentheses "()" shown after the symbols for particular amino acid residues indicate residues whose side chains participate in an intramolecular lactam bridge. Thus, petrelintide has an intramolecular lactam bridge between the side chains of the residues at position 2
35 (aspartic acid, D) and at position 7 (lysine, K) as indicated by parentheses.

Petrelintide

Petrelintide is an acylated peptide molecule that agonises amylin receptors. Petrelintide was first described in the patent application published as WO 2018/046719 A1 (which is incorporated herein by reference), wherein petrelintide was referred to as Compound 35.

- 5 Petrelintide may be referred to herein as Compound 35 or Cpd 35.

Petrelintide has the following formula:

[19CD]-isoGlu-RD()
GTATK()
ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTNT-Hyp-NH₂ (SEQ ID NO: 1)

- 10 wherein

[19CD]-isoGlu is a 19-carboxynonadecanoyl group covalently attached to the alpha amino group of an iso-glutamic acid linker;
an intramolecular lactam bridge is formed between the side chains of residues indicated by parentheses “()”;

- 15 Aad refers to 2-aminoadipic acid;
Gly(Me) refers to N-methylglycine;
Ile(Me) refers to N-methylisoleucine; and
Hyp refers to 4-hydroxyproline.

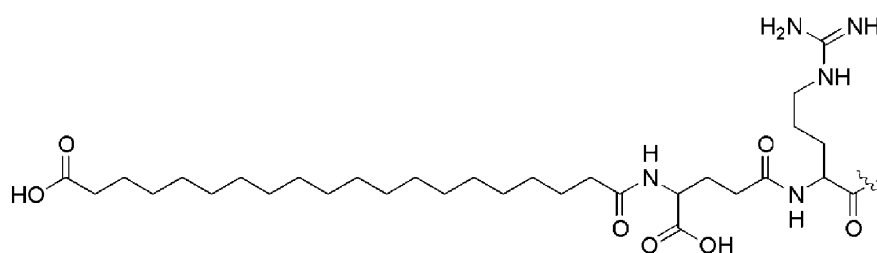
- 20 The formula of petrelintide may also be presented as follows:

[19CD]-isoGlu-RD(cyclo)
GTATK(cyclo)
ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTNT-Hyp-NH₂ (SEQ ID NO: 1)

wherein

- [19CD]-isoGlu is a 19-carboxynonadecanoyl group covalently attached to the alpha amino group of an iso-glutamic acid linker;
an intramolecular lactam bridge is formed between the side chains of residues followed by “(cyclo)”;
Aad refers to 2-aminoadipic acid;
Gly(Me) refers to N-methylglycine;
25 Ile(Me) refers to N-methylisoleucine; and
30 Hyp refers to 4-hydroxyproline.

The chemical structure of [19CD]-isoGlu- covalently attached to arginine is shown below:



Petrelintide is an amylin receptor agonist. In other words, petrelintide is capable of binding to, and inducing signalling by, one or more receptors or receptor complexes regarded as physiological receptors for human amylin. These include the human calcitonin receptor (hCT-R), as well as complexes comprising hCT-R and at least one of the human receptor activity modifying proteins designated hRAMP1, hRAMP2 and hRAMP3. Complexes between hCT-R and hRAMP1, hRAMP2 and hRAMP3 are designated hAMYR1, hAMYR2 and hAMYR3 (i.e. human amylin receptors 1, 2 and 3) respectively. Petrelintide has agonist activity at hAMYR1, hAMYR2 and hAMYR3 as described in WO 2018/046719 A1. Binding to a suitable receptor induces intracellular signalling, e.g. cyclic AMP production. *In vivo*, petrelintide has the biological activity of (inter alia) reducing food intake, promoting weight loss, and/or inhibiting or reducing weight gain. It may be employed for various therapeutic applications as described elsewhere in this specification and in WO 2018/046719 A1.

Petrelintide may suitably be manufactured by standard synthetic methods. Thus, petrelintide may be synthesized by, e.g., methods comprising synthesizing the peptide by standard solid-phase or liquid-phase methodology, either stepwise or by fragment assembly, and optionally isolating and purifying the final peptide product. In this context, reference may be made to WO 98/11125 or, *inter alia*, Fields, G.B. et al., "Principles and Practice of Solid-Phase Peptide Synthesis"; in: *Synthetic Peptides*, Gregory A. Grant (ed.), Oxford University Press (2nd edition, 2002) and the synthesis examples herein. The method typically further comprises the step of forming an amide bond between the side chains at positions 2 and 7, e.g. as described below. In the case of solid phase synthesis, cyclisation may be performed in situ on the solid phase (e.g. resin), i.e. before removal of the peptide from the solid phase. Synthesis of petrelintide is described in Example 1 of WO 2018/046719 A1.

Pharmaceutically acceptable salts or solvates

Petrelintide as used in the invention may be in the form of a pharmaceutically acceptable salt or solvate, such as a pharmaceutically acceptable acid addition salt. Thus, it is to be understood that any reference herein to petrelintide encompasses pharmaceutically acceptable salts and solvates thereof.

As used herein, the term "pharmaceutically acceptable salt" is intended to indicate a salt which is not harmful to a patient or subject to which the salt in question is administered. It may suitably be a salt chosen, e.g., among acid addition salts and basic salts. Suitable salts
5 formed with bases include metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts; ammonia salts and organic amine salts, such as those formed with morpholine, thiomorpholine, piperidine, pyrrolidine, a lower mono-, di- or tri-alkylamine (e.g., ethyl-tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine), or a lower mono-, di- or tri-(hydroxyalkyl)amine (e.g., mono-, di- or
10 triethanolamine). Internal salts may also be formed. Similarly, when a compound of the present invention contains a basic moiety, salts can be formed using organic or inorganic acids. For example, salts can be formed from the following acids: formic, acetic, propionic, butyric, valeric, caproic, oxalic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric, benzoic,
15 carbonic, uric, methanesulphonic, naphthalenesulphonic, benzenesulphonic, toluenesulphonic, p-toluenesulphonic (i.e. 4-methylbenzene-sulphonic), camphorsulphonic, 2-aminoethanesulphonic, aminomethylphosphonic and trifluoromethanesulphonic acid (the latter also being denoted triflic acid), as well as other known pharmaceutically acceptable acids. Amino acid addition salts can also be formed with amino acids, such as lysine,
20 glycine, or phenylalanine. Other examples of pharmaceutically acceptable salts are described in "Remington's Pharmaceutical Sciences", 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the "Encyclopaedia of Pharmaceutical Technology", 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, and in *J. Pharm. Sci.* 66: 2 (1977).

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Petrelintide may be in the form of a pharmaceutically acceptable chloride salt. In some embodiments, petrelintide may have the formula

$$([^{19}\text{CD}]\text{-isoGlu-RD}(\text{)}\text{GTATK}(\text{)}\text{ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsNT-Hyp-NH}_2), x(\text{Cl})$$

30 where x is 1.0-2.0.

The term "solvate" in the context of the present invention refers to a complex of defined stoichiometry formed between a solute (*in casu*, a peptide or pharmaceutically acceptable salt thereof according to the invention) and a solvent. The solvent in this connection may, for
35 example, be water, ethanol or another pharmaceutically acceptable, typically small-molecular organic species, such as, but not limited to, acetic acid or lactic acid. When the solvent in question is water, such a solvate is normally referred to as a hydrate.

Reducing body fat whilst preserving lean mass

The invention provides a method of reducing body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a
5 pharmaceutically acceptable salt or solvate thereof.

The amount of body fat (and accordingly lean mass) in a given subject may be determined by methods known in the art. Such methods include skinfold tests, bioelectrical impedance analysis, hydrostatic weighing, dual-energy X-ray absorptiometry (DEXA), quantitative
10 magnetic resonance (QMR) and air-displacement plethysmography (ADP). Examples of use of DEXA and QMR in animal models are described in, for example, Miller et al. *Physiol Behav* 2011 103(1) 117-121. ADP is described, for example, in the review article Fields et al. *Nutr Clin Pract* 2015 30(2) 219-226. EchoMRI™ is a commercially available type of QMR used in Example 1 herein. The BOD POD® (COSMED, Rome, Italy) is a commercially
15 available measurement system for performing ADP used in Example 3 herein.

Methods and uses of the present invention are carried out *in vivo*.

Suppression of glucagon secretion and food intake associated with petrelintide may promote
20 weight loss, or at least slow (i.e. reduce or inhibit) weight gain. Thus, the method of the invention may be expressed as a method of inhibiting or reducing weight gain, a method of promoting weight loss, a method of reducing food intake, and/or a method of reducing body weight in a subject, wherein lean mass is preserved in the subject.

25 Accordingly, the invention provides a method of reducing body mass whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of inhibiting weight gain whilst preserving lean mass in
30 a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of inhibiting gain of body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a
35 pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of promoting weight loss whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

- 5 The terms “inhibiting weight gain” and “inhibiting gain of body fat” are used interchangeably herein.

The term “body fat” refers to adipose tissue, which is the type of tissue which stores fat in the body. Body fat includes so-called “brown fat”, “beige fat” “white fat” and “pink fat”. Body fat
10 includes particularly subcutaneous adipose tissue that stores excess fat, such as in the belly, thighs and hips of human subjects.

The term “lean mass” refers to all mass of a subject which is not body fat. Lean mass may also be referred to as “fat-free mass”. “Lean mass” primarily includes the combined mass of
15 muscle, bone, viscera (i.e. organs such as heart, lungs, gastrointestinal tract etc.) and other tissues such as arteries, veins, lymph nodes etc.

It is well-understood both medically and by laypersons that excess fat can be undesirable for medical reasons (such as in overweight, obese or morbidly obese subjects) or for cosmetic
20 reasons (such as in subjects of a healthy weight). The central concept of the present invention is that use of petrelintide can reduce unwanted body fat without reducing desirable lean mass, in particular muscle. The terms “body fat” and “lean mass” are used in that context herein, to indicate the types of mass which it is typically desirable to lose (body fat) or retain (lean mass, particularly muscle) when losing weight.

25 Thus, the term “preserving lean mass” means to prevent or avoid loss of lean mass. In quantitative terms, preserving lean mass means that lean mass of the subject increases or does not change or, of lean mass of the subject decreases, then it does so only to an insignificant degree. Accordingly, a method of the invention may also be expressed as a
30 method of reducing body fat whilst preventing loss of lean mass in a subject or a method of reducing body fat whilst avoiding loss of lean mass in a subject.

Reducing body fat

The amount of body fat of a subject may be expressed in absolute terms, i.e., in grams (g) or
35 kilograms (kg) or as a percentage of the total body weight of the subject (%bw). The percentage of the total body weight of the subject (%bw) that is body fat is referred to herein as “%bw body fat” or “body fat composition (%bw)”. A change in body fat, such as a

reduction in body fat, is expressed herein as a % change (i.e. %bw body fat change) over time.

5 In some embodiments, as a result of the method of the invention, the body fat of the subject is reduced by at least about 1%. In some embodiments, the body fat of the subject is reduced by at least about 2%, such as at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, or at least about 50%.

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In some embodiments, as a result of the method of the invention, the body fat of the subject is reduced by up about 5%, up to about 6%, up to about 7%, up to about 8%, up to about 9%, up to about 10%, up to about 15%, up to about 20%, up to about 25%, up to about 30%, up to about 40%, or up to about 50%.

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In some embodiments, as a result of the method of the invention, the body fat of the subject is reduced by about 1%. In some embodiments, the body fat of the subject is reduced by about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, or about 50%.

20

In some embodiments, as a result of the method of the invention, the body fat of the subject is reduced by from about 1% to about 50%, by from about 5% to about 50%, by from about 10% to about 50%, by from about 20% to about 50%, by from about 30% to about 50%, or , by from about 40% to about 50%.

25

In some embodiments, as a result of the method of the invention, the body fat of the subject is reduced by from about 1% to about 40%, by from about 5% to about 40%, by from about 10% to about 40%, by from about 20% to about 40%, or by from about 30% to about 40%.

30 To determine whether and by how much body fat of the subject has been reduced, body fat of the subject is measured over time. In other words, in some embodiments, as a result of the method of the invention, the body fat of the subject is reduced by a given amount over a given period (i.e. the body fat of the subject at the end of the period differs from the body fat of the subject at the start of the period by a given amount).

35

In some embodiments, the body fat of the subject is reduced over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least

about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

- 5 In some embodiments, the body fat of the subject is reduced over a period of more than 10 years.

In some embodiments, the body fat of the subject is reduced over a period of about 1 week. In some embodiments, the body fat of the subject is reduced over a period of about 30 days.

- 10 In some embodiments, the body fat of the subject is reduced over a period of about 1 month. In some embodiments, the body fat of the subject is reduced over a period of about 6 months. In some embodiments, the body fat of the subject is reduced over a period of about 1 year. In some embodiments, the body fat of the subject is reduced over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.

- 20 In some embodiments, the body fat of the subject is reduced by at least about 1% over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

- 25 In some embodiments, the body fat of the subject is reduced by at least about 1% over a period of about 1 week. In some embodiments, the body fat of the subject is reduced by at least about 1% over a period of about 30 days. In some embodiments, the body fat of the subject is reduced by at least about 1% over a period of about 1 month. In some embodiments, the body fat of the subject is reduced by at least about 1% over a period of about 6 months. In some embodiments, the body fat of the subject is reduced by at least about 1% over a period of about 1 year, about 2 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.

- 35 In some embodiments, the body fat of the subject is reduced by at least about 2% over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at

least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 2% over a
5 period of about 1 week. In some embodiments, the body fat of the subject is reduced by at least about 2% over a period of about 30 days. In some embodiments, the body fat of the subject is reduced by at least about 2% over a period of about 1 month. In some
embodiments, the body fat of the subject is reduced by at least about 2% over a period of
about 6 months. In some embodiments, the body fat of the subject is reduced by at least
10 about 2% over a period of about 1 year.

In some embodiments, the body fat of the subject is reduced by at least about 5% over a
period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least
about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at
15 least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at
least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or
at least about 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 5% over a
20 period of more than 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 5% over a
period of about 6 months. In some embodiments, the body fat of the subject is reduced by at
least about 5% over a period of about 1 year, about 2 years, about 5 years, about 6 years,
25 about 7 years, about 8 years, about 9 years, or about 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 10% over a
period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least
about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at
30 least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at
least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or
at least about 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 10% over a
35 period of more than 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 10% over a period of about 6 months. In some embodiments, the body fat of the subject is reduced by at least about 10% over a period of about 1 year, about 2 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.

5

In some embodiments, the body fat of the subject is reduced by at least about 10% over a period of about 1 year.

10 In some embodiments, the body fat of the subject is reduced by at least about 1% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

15 In some embodiments, the body fat of the subject is reduced by at least about 2% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

20 In some embodiments, the body fat of the subject is reduced by at least about 3% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 4% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

25 In some embodiments, the body fat of the subject is reduced by at least about 5% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

30 In some embodiments, the body fat of the subject is reduced by at least about 6% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

35 In some embodiments, the body fat of the subject is reduced by at least about 7% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

In some embodiments, the body fat of the subject is reduced by at least about 8% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

- 5 In some embodiments, the body fat of the subject is reduced by at least about 9% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

- 10 In some embodiments, the body fat of the subject is reduced by at least about 10% over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

Preserving lean mass

- 15 As body fat decreases whilst lean mass is preserved, the ratio of lean mass to body fat of the subject increases. Therefore, a method of the invention may be expressed as a method of increasing the ratio of lean mass to body fat in the subject. In some embodiments, the method is a method of increasing the ratio of muscle to body fat in the subject.
- 20 The amount of lean mass of a subject may be expressed in absolute terms, i.e., in grams (g) or kilograms (kg) or as a percentage of the total body weight of the subject (%bw). The percentage of the total body weight of the subject (%bw) that is lean mass is referred to herein as "%bw lean mass" or "lean mass composition (%bw)". A change in lean mass, such as an increase in lean mass, is expressed herein as a % change (i.e. %bw lean mass
- 25 change) over time.

In some embodiments, as a result of the method of the invention, the lean mass of the subject is reduced insignificantly, or does not change, or increases.

- 30 In some embodiments, the lean mass of the subject is reduced insignificantly. The lean mass of the subject being reduced "insignificantly" means a reduction of less than about 1% lean mass.

- In some embodiments, the lean mass of the subject does not change. The lean mass of the
- 35 subject not changing means a change of from -0.1% to +0.1% lean mass.

In some embodiments, the lean mass of the subject increases. In some embodiments, the % lean mass of the subject increases. It will be understood that if a subject loses body fat at a greater rate than lean mass, the % lean mass may increase, even if the absolute amount of lean mass remains constant, because the remaining lean mass makes up a larger proportion of the total body mass than before the loss of body fat.

In some embodiments, as a result of the method of the invention the lean mass of the subject is reduced by less than about 1%, such as by about 0%.

In some embodiments, as a result of the method of the invention the whole body lean mass of the subject increases by at least about 0.1%, such as by at least about 0.2%, at least about 0.3%, at least about 0.4%, at least about 0.5%, at least about 0.6%, at least about 0.7%, at least about 0.8%, at least about 0.9%, at least about 1.0%, at least about 1.1%, at least about 1.2%, at least about 1.3%, at least about 1.4%, at least about 1.5%, at least about 1.6%, at least about 1.7%, at least about 1.8%, at least about 1.9%, at least about 2.0%, at least about 2.5%, at least about 3%, at least about 4%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100%.

In some embodiments, as a result of the method of the invention the whole body lean mass of the subject increases by about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, or about 2.0%, about 2.5%, about 3%, about 4%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

To determine whether and by how much lean mass of the subject has changed, lean mass of the subject is measured over time. In other words, in some embodiments, as a result of the method of the invention, the lean mass of the subject changes by a given amount (or does not change, if that amount is 0) over a given period (i.e. the lean mass of the subject at the end of the period differs from the lean mass of the subject at the start of the period by a given amount).

In some embodiments, as a result of the method of the invention, the lean mass of the subject increases over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at
5 least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

In some embodiments, as a result of the method of the invention, the lean mass of the
10 subject increases over a period of more than 10 years.

In some embodiments, as a result of the method of the invention, the lean mass of the subject increases over a period of about 1 week. In some embodiments, the lean mass of the subject increases over a period of about 30 days. In some embodiments, the lean mass
15 of the subject increases over a period of about 1 month. In some embodiments, the lean mass of the subject increases over a period of about 6 months. In some embodiments, the lean mass of the subject increases over a period of about 1 year. In some embodiments, the lean mass of the subject increases over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months,
20 about 6 months, about 1 year, about 2 years, about 5 years or about 10 years or more.

In some embodiments, as a result of the method of the invention, the lean mass of the subject does not change over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month,
25 at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

In some embodiments, as a result of the method of the invention, the lean mass of the
30 subject does not change over a period of more than 10 years.

In some embodiments, as a result of the method of the invention, the lean mass of the subject does not change over a period of about 1 week. In some embodiments, the lean mass of the subject does not change over a period of about 30 days. In some embodiments,
35 the lean mass of the subject does not change over a period of about 1 month. In some embodiments, the lean mass of the subject does not change over a period of about 6 months. In some embodiments, the lean mass of the subject does not change over a period

of about 1 year. In some embodiments, the lean mass of the subject does not change over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years or more.

5

To determine whether a given use of petrelintide has reduced body fat whilst preserving lean mass, the change in body fat and change in lean mass in the subject should be measured over the same time period. In this way, it is possible to determine that body fat has indeed reduced whilst no change or an increase of lean mass has occurred.

10

Thus, in some embodiments, the change in body fat and lean mass are measured over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

15

In some embodiments, the change in body fat and lean mass are measured over a period of more than 10 years.

20

Thus, in some embodiments, the change in body fat and lean mass are measured over a period of about 1 week. In some embodiments, the change in body fat and lean mass are measured over a period of about 30 days. In some embodiments, the change in body fat and lean mass are measured over a period of about 1 month. In some embodiments, the change in body fat and lean mass are measured over a period of about 6 months. In some embodiments, the change in body fat and lean mass are measured over a period of about 1 year. In some embodiments, the change in body fat and lean mass are measured over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

25

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Reducing body weight

The invention provides petrelintide for use in a method of inhibiting weight gain and/or reducing body weight in a subject.

35

In other words, the methods and uses of the invention may be expressed as methods and uses of inhibiting weight gain and/or reducing body weight in the subject.

Thus, the invention provides a method of inhibiting weight gain and/or reducing body weight whilst preserving lean mass in a subject, wherein the method comprises administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

5

"Inhibiting weight gain" may also be referred to as "reducing weight gain". "Reducing body weight" may also be referred to as "promoting weight loss".

Petrelintide may increase or prolong the feeling of satiation experienced by a subject, thereby reducing the appetite of the subject, leading to reduced food intake. Thus, the invention may be expressed as petrelintide for use in a method of reducing food intake and/or reducing appetite and/or increasing satiety.

In some embodiments, the method of the invention is a method of reducing food intake.
In some embodiments, the method of the invention is a method of reducing appetite.
In some embodiments, the method of the invention is a method of increasing satiety.

Petrelintide may be used for therapeutic or cosmetic purposes. Thus, the inhibition of weight gain or reduction of body weight of the subject may be cosmetic (i.e. non-therapeutic).
Effects of petrelintide on body weight may be therapeutic or cosmetic.

The invention further relates to petrelintide for use in methods that are not directed towards treating disease *per se*. Such uses and methods may be considered preventative of disease in so far as they may be utilised prior to the onset of disease (e.g. pre diagnosis) e.g. to ameliorate unwanted physiological characteristics or alter certain physiological parameters. Furthermore, such uses or methods may be considered cosmetic.

The effects of petrelintide may be mediated in whole or in part via an effect on body weight, or may be independent thereof. Independently of the effect of petrelintide on body weight, petrelintide may have a beneficial effect on glucose tolerance and/or glucose control.

In some embodiments, the subject exhibits a reduction in body weight upon treatment with petrelintide. In some embodiments, the subject exhibits a reduction in body weight of at least 1%, such as at least 5%, at least 10%, at least 15%, at least 20%, at least 22.5% or at least 25%, compared to their body weight before treatment. In some embodiments, the subject exhibits a reduction in body weight of at least 0.5% per month (i.e. 0.5% reduction in body weight at the end of each month compared to body weight at the start of the month), such as

at least 0.75% per month, at least 1% per month, at least 1.25% per month or at least 1.3% per month. In some embodiments, the subject exhibits a reduction in body weight of 0.5% per month, 0.75% per month, 1% per month, 1.25% per month or 1.3% per month.

5 ***Preserving muscle***

The most important constituent of lean mass in the context of the present invention is muscle (i.e. muscle mass). The mass of both subcutaneous adipose tissue and muscle tissue may be reduced upon weight loss (particularly weight loss through calorific restriction without associated exercise). It is desirable to avoid loss of muscle during weight loss due to the
10 functional and perceived cosmetic benefits therefrom.

Accordingly, the methods of the invention may also be expressed as methods of reducing body fat whilst preserving muscle in a subject.

15 Methods for measuring muscle mass are known in the art. Such methods include computed tomography (CT) scan, Magnetic Resonance Imaging (MRI) and air-displacement plethysmography (ADP). ADP is described, for example, in the review article Fields et al. Nutr Clin Pract 2015 30(2) 219-226. Examples of methods for measuring muscle mass in obese human subjects are described in, for example, Sizoo et al. Obes Surg. 2020 31(1)
20 384–393. The BOD POD® (COSMED, Rome, Italy) is a commercially available measurement system for performing ADP used in Example 3 herein.

Practically, preserving muscle in a subject means preserving the mass of the muscle (i.e., preventing loss of muscle mass). Hence, the expression “preserving muscle” as used herein
25 is interchangeable with the expressions “preserving muscle mass”, “preventing loss of muscle mass”, “avoiding loss of muscle” and “avoiding loss of muscle mass”.

The terms “muscle” and “muscle mass” refer to the overall muscle mass of the subject. The mass of particular muscles will necessarily be preserved by the methods and uses of the
30 invention, but the methods and uses of the invention are not limited to preservation of the mass of particular muscles. Rather, it is the muscle mass of the subject as a whole that is preserved.

Thus, the invention provides a method of reducing body fat whilst preserving muscle in a
35 subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof. The methods of the invention may be expressed as methods of reducing body fat whilst preserving overall muscle mass in a

subject. The methods of the invention may be expressed as methods of reducing body fat whilst preserving whole body muscle mass in a subject.

5 The invention also provides a method of reducing body mass whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

10 The invention also provides a method of inhibiting weight gain whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

15 The invention also provides a method of inhibiting gain of body fat whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of promoting weight loss whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

20 "Preserving muscle" may mean that there is no loss of muscle mass due to administration of petrelintide in accordance with the invention.

"Preserving muscle" also encompasses an increase in muscle mass during the period of administration of petrelintide in accordance with the invention.

25 "Preserving muscle" also encompasses a situation wherein muscle mass decreases during the period of administration of petrelintide in accordance with the invention, but wherein the decrease in muscle mass is less (i.e., less severe, i.e., not as great a loss of muscle mass) than when body weight is reduced by an alternative method over the same period.

30 Thus, "preserving muscle" may mean reducing or inhibiting loss of muscle mass.

35 Accordingly, the invention provides a method of reducing body fat whilst inhibiting loss of muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof. The invention provides a method of reducing body fat whilst reducing loss of muscle in a subject, the method comprising

administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The loss of muscle mass when the subject is administered petrelintide may be less than
5 when the subject loses body fat by calorific restriction, or by administration of a different active, such as a glucagon-like peptide 1 receptor (GLP-1R) agonist. GLP-1R agonists include semaglutide, tirzepatide (which also is also a gastric inhibitory peptide receptor (GIPR) agonist) and liraglutide.

10 Thus, in some embodiments, the invention provides a method of reducing body fat whilst reducing loss of muscle mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof. In some
15 embodiments, the loss of muscle mass in the subject is less than when the subject loses body fat by calorific restriction over the same length of time. In some embodiments, the loss of muscle mass in the subject is less than when the subject loses body fat due to administration to the subject of liraglutide over the same length of time. In some
20 embodiments, the loss of muscle mass in the subject is less than when the subject loses body fat due to administration to the subject of semaglutide over the same length of time. In some embodiments, the loss of muscle mass in the subject is less than when the subject loses body fat due to administration to the subject of tirzepatide over the same length of time.

The muscle mass of a subject may be expressed in absolute terms, i.e., in grams (g) or kilograms (kg) or as a percentage of the total body weight of the subject (%bw). The
25 percentage of the total body weight of the subject (%bw) that is muscle is referred to herein as "%bw muscle mass" or "muscle mass composition (%bw)". A change in muscle mass, such as an increase in muscle mass, is expressed herein as a % change (i.e. %bw muscle mass change) over time.

30 In some embodiments, as a result of the method of the invention, the muscle mass of the subject is reduced insignificantly, or does not change, or increases.

In some embodiments, the muscle mass of the subject is reduced insignificantly. The muscle mass of the subject being reduced "insignificantly" means a reduction of less than about 1%
35 muscle mass.

In some embodiments, the muscle mass of the subject does not change. The muscle mass of the subject not changing means a change of from -0.1% to +0.1% muscle mass.

5 In some embodiments, the muscle mass of the subject increases. In some embodiments, the % muscle mass of the subject increases. It will be understood that if a subject loses body fat at a greater rate than muscle mass, the % muscle mass may increase, even if the absolute muscle mass remains constant, because the remaining muscle mass makes up a larger proportion of the total body mass than before the loss of body fat.

10 In some embodiments, as a result of the method of the invention the muscle mass of the subject is reduced by less than about 1%, such as by about 0%.

In some embodiments, as a result of the method of the invention the whole body muscle mass of the subject increases by at least about 0.1%, such as by at least about 0.2%, at
15 least about 0.3%, at least about 0.4%, at least about 0.5%, at least about 0.6%, at least about 0.7%, at least about 0.8%, at least about 0.9%, at least about 1.0%, at least about 1.1%, at least about 1.2%, at least about 1.3%, at least about 1.4%, at least about 1.5%, at least about 1.6%, at least about 1.7%, at least about 1.8%, at least about 1.9%, or at least about 2.0%.

20

To determine whether and by how much muscle mass of the subject has changed, muscle mass of the subject is measured over time. In other words, in some embodiments, as a result of the method of the invention, the muscle mass of the subject changes by a given amount (or does not change, if that amount is 0) over a given period (i.e. the muscle mass of
25 the subject at the end of the period differs from the muscle mass of the subject at the start of the period by a given amount).

In some embodiments, as a result of the method of the invention, the muscle mass of the subject increases over a period of at least about 1 week, at least about 2 weeks, at least
30 about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

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In some embodiments, as a result of the method of the invention, the muscle mass of the subject increases over a period of more than 10 years,

In some embodiments, as a result of the method of the invention, the muscle mass of the subject increases over a period of about 1 week. In some embodiments, the muscle mass of the subject increases over a period of about 30 days. In some embodiments, the muscle mass of the subject increases over a period of about 1 month. In some embodiments, the muscle mass of the subject increases over a period of about 6 months. In some embodiments, the muscle mass of the subject increases over a period of about 1 year. In some embodiments, the muscle mass of the subject increases over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

In some embodiments, as a result of the method of the invention, the muscle mass of the subject does not change over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

In some embodiments, as a result of the method of the invention, the muscle mass of the subject does not change over a period of more than 10 years,

In some embodiments, as a result of the method of the invention, the muscle mass of the subject does not change over a period of about 1 week. In some embodiments, the muscle mass of the subject does not change over a period of about 30 days. In some embodiments, the muscle mass of the subject does not change over a period of about 1 month. In some embodiments, the muscle mass of the subject does not change over a period of about 6 months. In some embodiments, the muscle mass of the subject does not change over a period of about 1 year. In some embodiments, the muscle mass of the subject does not change over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

To determine whether a given use of petrelintide has reduced body fat whilst preserving muscle mass, the change in body fat and change in muscle mass in the subject should be

measured over the same time period. In this way, it is possible to determine that body fat has indeed reduced whilst no change or an increase of muscle mass has occurred.

Thus, in some embodiments, the change in body fat and muscle mass are measured over a period of at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, or at least about 10 years.

In some embodiments, the change in body fat and muscle mass are measured over a period of more than 10 years,

In some embodiments, as a result of the method of the invention, the change in body fat and lean muscle are measured over a period of about 1 week. In some embodiments, the change in body fat and muscle mass are measured over a period of about 30 days. In some embodiments, the change in body fat and muscle mass are measured over a period of about 1 month. In some embodiments, the change in body fat and muscle mass are measured over a period of about 6 months. In some embodiments, the change in body fat and muscle mass are measured over a period of about 1 year. In some embodiments, the change in body fat and muscle mass are measured over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 5 years or about 10 years.

Subject

The terms "patient", "subject", "participant", and "individual" are used interchangeably herein and refer to either a human or a non-human animal. These terms include mammals such as humans, non-human primates (e.g. great apes, Old World monkeys and New World monkeys), livestock animals (e.g. bovines and porcines), companion animals (e.g. canines and felines) and rodents (e.g. mice and rats). Preferably, the subject is human.

In some embodiments of the methods of treatment and medical uses of the invention, the subject is of a healthy weight. In other words, in some embodiments, the subject is not overweight, not obese and not morbidly obese.

In some embodiments, the subject has a Body Mass Index (BMI) of 18.5 to 24.9 corresponding to healthy weight.

BMI is calculated for human subjects by dividing the weight of the subject in kilograms by the square of the height of the subject in metres.

- 5 In some embodiments of the methods of treatment and medical uses of the invention, wherein the subject is overweight, obese or morbidly obese.

In some embodiments, the subject is overweight.

In some embodiments, the subject is obese.

In some embodiments, the subject is morbidly obese.

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In some embodiments of the methods of treatment and medical uses of the invention, the subject has a BMI of 25.0 to 29.9 corresponding to overweight, a BMI of 30.0 to 39.9 corresponding to obese, or a BMI of 40.0 or higher corresponding to morbidly obese.

In some embodiments, the subject has a BMI of 25.0 to 29.9 corresponding to overweight.

- 15 In some embodiments, the subject has a BMI of 30.0 to 39.9 corresponding to obese.

In some embodiments, the subject has a BMI of 40.0 or higher corresponding to morbidly obese.

Non-therapeutic uses

- 20 The methods of reducing body fat whilst preserving lean mass of the invention may be non-therapeutic methods. In other words, petrelintide may be used for non-therapeutic purposes.

In this respect, it may be desirable for a subject to reduce food intake so as to lose weight (or inhibit weight gain), and thereby reduce body fat, despite the subject not being obese,

- 25 diabetic or suffering from any other weight-related disease, such as for cosmetic reasons.

Administration of petrelintide may achieve these desired effects (reduced food intake, weight loss and/or inhibited weight gain). In such embodiments, administration of petrelintide would not be therapeutic as no disease or disorder is being treated by petrelintide.

- 30 Thus, in some embodiments, the method of the invention is a non-therapeutic method.

The invention therefore provides a non-therapeutic method of reducing body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

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The invention also provides a non-therapeutic method of inhibiting weight gain whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

- 5 The non-therapeutic nature of certain methods of the invention is particularly pertinent when the subject is of healthy weight or overweight (i.e. a subject that is not obese or morbidly obese). Obesity and morbid obesity may be considered disease states, whereas healthy weight and overweight may be considered simply descriptive of the body weight of the subject. Administration of petrelintide to a subject that is a healthy weight or that is
- 10 overweight, for which there are no therapeutic reasons to reduce body fat, is a cosmetic (non-therapeutic) method. Petrelintide is of particular use for this purpose as petrelintide reduces body fat whilst preserving lean mass, such as muscle, which may be particularly desired for cosmetic purposes.
- 15 The invention therefore provides a non-therapeutic method of reducing body fat whilst preserving lean mass in a subject of healthy weight, the method comprising administering to the subject an amylin analogue or a pharmaceutically acceptable salt or solvate thereof, wherein the amylin analogue is as defined herein.
- 20 The invention also provides a non-therapeutic method of inhibiting weight gain whilst preserving lean mass in a subject of healthy weight, the method comprising administering to the subject an amylin analogue or a pharmaceutically acceptable salt or solvate thereof, wherein the amylin analogue is as defined herein.
- 25 Body weight is defined in the medical field by body mass index (BMI). BMI is calculated for human subjects by dividing the weight of the subject in kilograms by the square of the height of the subject in metres. A BMI of 18.5 to 24.9 corresponds to healthy weight. A BMI of 25.0 to 29.9 corresponds to overweight. Thus, in some embodiments of the non-therapeutic (i.e., cosmetic) methods of the invention, the subject has a Body Mass Index (BMI) of 18.5 to 24.9
- 30 corresponding to healthy weight. In some embodiments of the non-therapeutic (i.e., cosmetic) methods of the invention, the subject has a BMI of 25.0 to 29.9 corresponding to overweight.

- In other words, the subject of a non-therapeutic method of the invention of reducing body or
- 35 inhibiting weight gain whilst preserving lean mass need not be obese or morbidly obese.

The invention therefore provides a non-therapeutic method of reducing body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

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The invention also provides a non-therapeutic method of reducing body mass whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

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The invention also provides a non-therapeutic method of inhibiting weight gain whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

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The invention also provides a non-therapeutic method of inhibiting gain of body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

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The invention also provides a non-therapeutic method of promoting weight loss whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

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The invention therefore provides a non-therapeutic method of reducing body fat whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

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The invention also provides a non-therapeutic method of reducing body mass whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

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The invention also provides a non-therapeutic method of inhibiting weight gain whilst preserving muscle in a subject, the method comprising administering to the subject

petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

5 The invention also provides a non-therapeutic method of inhibiting gain of body fat whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

10 The invention also provides a non-therapeutic method of promoting weight loss whilst preserving muscle in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof, wherein the subject is a healthy weight or is overweight.

15 Considerations regarding petrelintide as outlined herein apply equally when petrelintide is used for therapeutic and non-therapeutic purposes.

Therapeutic uses

20 In accordance with the surprising finding that petrelintide reduces body fat whilst preserving lean mass, petrelintide has utility in a number of therapeutic settings. Petrelintide is useful in the treatment or prevention of disease.

25 More specifically, petrelintide is useful, *inter alia*, in the reduction of food intake, promotion of weight loss, and inhibition or reduction of weight gain. Petrelintide may therefore provide an attractive treatment option for, *inter alia*, obesity and metabolic diseases caused, characterized by, or associated with, excess body weight. Treatment may be achieved, for example, by control of appetite, feeding, food intake, calorie intake and/or energy expenditure.

30 The term "treatment" (as well as "treating" and other grammatical variants thereof) as employed in the context of the invention refers to an approach for obtaining beneficial or desired clinical results. For the purposes of the present invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilization of (i.e. not worsening of) state of disease, delay or slowing of disease progression, amelioration or palliation of disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" may also refer to prolongation of survival compared to expected survival in the absence of treatment. "Treatment" is an intervention performed with the intention of preventing the development of,

or altering the pathology of, a disorder. Accordingly, "treatment" refers both to therapeutic treatment and to prophylactic or preventative measures. As used in the context of prophylactic or preventative measures, the amylin analogue or concomitant agent need not completely prevent the development of the disease or disorder. Those in need of treatment
5 include those already suffering from the disorder, as well as those in which development of the disorder is to be prevented. "Treatment" also means inhibition or reduction of an increase in pathology or symptoms (e.g. weight gain or hypoglycaemia) compared to the absence of treatment, and is not necessarily meant to imply complete cessation or cure of the relevant condition. The term "prevention" (as well as "preventing" and other grammatical
10 variants thereof) refers to prophylaxis of disease, such as by reducing symptoms of disease.

The terms "prevention" and grammatical variants thereof (e.g., "prevented", "preventing", "prevent") as employed in the present context refer to an approach for hindering or preventing the development of, or altering the pathology of, a condition, disease or disorder.
15 Accordingly, "prevention" may refer to prophylactic or preventive measures. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, prevention or slowing of symptoms, progression or development of a disease, whether detectable or undetectable. A subject (e.g. a human) in need of "prevention" may thus be a subject not yet afflicted with the disease or disorder in question. The term "prevention" thus
20 includes inhibiting or slowing the onset of disease relative to the absence of treatment, and is not necessarily meant to imply permanent prevention of the relevant disease, disorder or condition. In some embodiments, "prevention" or "prophylaxis" in the context of the present invention may mean prevention of weight gain (i.e. inhibiting weight gain). In some
25 embodiments, "prevention" or "prophylaxis" may mean prevention of gain of body fat.

Methods of treatment

Therapeutic methods (i.e. methods of treating or preventing disease) are within the scope of the methods of reducing body fat or inhibiting weight gain whilst preserving lean mass of the invention, as described herein.
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Thus, the invention provides a therapeutic method of reducing body fat whilst preserving lean mass in a subject, wherein the method treats or prevents a disease in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.
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The invention also provides a therapeutic method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the method treats or prevents a disease in the subject, the

method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Furthermore, the invention provides a method of treating or preventing overweight, obesity, morbid obesity or a disease associated with overweight, obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Thus, the methods of the invention, when applied to a subject that is overweight, obese, morbidly obese or suffers from a disease associated with overweight, obesity or morbid obesity, may be considered therapeutic methods.

However, for a method of the invention to be therapeutic it is not required that the subject is overweight, obese or morbidly obese. It will be understood in particular that in a method of the invention of inhibiting weight gain whilst preserving lean mass, the subject need not be overweight, obese or morbidly obese. Such a method may be prophylactic in that it prevents (i.e. inhibits) weight gain as part of treatment of the disease from which the subject suffers.

The invention provides a method of treating overweight, obesity, morbid obesity or a disease associated with overweight, obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of preventing overweight, obesity, morbid obesity or a disease associated with overweight, obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of treating or preventing overweight, obesity or morbid obesity in a subject, or preventing a disease associated with overweight, obesity or morbid obesity, in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Furthermore, the invention provides a method of treating or preventing obesity, morbid obesity or a disease associated with obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of treating obesity, morbid obesity or a disease associated with obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of preventing obesity, morbid obesity or a disease associated with obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of treating or preventing obesity or morbid obesity in a subject, or preventing a disease associated with obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Furthermore, the invention provides a method of treating or preventing obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the method is a method of treating or preventing overweight.
In some embodiments, the method is a method of treating overweight.
In some embodiments, the method is a method of preventing overweight.

In some embodiments, the method is a method of treating or preventing obesity.
In some embodiments, the method is a method of treating obesity.
In some embodiments, the method is a method of preventing obesity.

In some embodiments, the method is a method of treating or preventing morbid obesity.
In some embodiments, the method is a method of treating morbid obesity.

In some embodiments, the method is a method of preventing morbid obesity.

Medical uses

The methods of the invention described herein may also be expressed as medical uses of
5 petrelintide.

Accordingly, the invention provides an petrelintide or a pharmaceutically acceptable salt or
solvate thereof for use in a method of reducing body fat whilst preserving lean mass in a
subject, the method comprising administering to the subject petrelintide or pharmaceutically
10 acceptable salt or solvate thereof.

The invention also provides petrelintide or a pharmaceutically acceptable salt or solvate
thereof for use in a method of inhibiting weight gain whilst preserving lean mass in a subject,
the method comprising administering to the subject petrelintide or pharmaceutically
15 acceptable salt or solvate thereof.

The invention also provides petrelintide or a pharmaceutically acceptable salt or solvate
thereof for use in a method of treating or preventing overweight, obesity, morbid obesity or a
disease associated with overweight, obesity or morbid obesity in a subject, wherein the
20 method reduces body fat whilst preserving lean mass in the subject.

The invention also provides petrelintide or a pharmaceutically acceptable salt or solvate
thereof for use in a method of treating or preventing obesity, morbid obesity or a disease
associated with obesity or morbid obesity in a subject, wherein the method reduces body fat
25 whilst preserving lean mass in the subject.

The invention also provides petrelintide or a pharmaceutically acceptable salt or solvate
thereof for use in a method of treating or preventing obesity or morbid obesity in a subject,
wherein the method reduces body fat whilst preserving lean mass in the subject.
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The invention also provides use of petrelintide or a pharmaceutically acceptable salt or
solvate thereof in preparation of a medicament for a method of treating or preventing
overweight, obesity, morbid obesity or a disease associated with overweight, obesity or
morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean
35 mass in the subject.

The invention also provides use of petrelintide or a pharmaceutically acceptable salt or solvate thereof in preparation of a medicament for a method of treating or preventing obesity, morbid obesity or a disease associated with obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject.

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The invention also provides use of petrelintide or a pharmaceutically acceptable salt or solvate thereof in preparation of a medicament for a method of treating or preventing obesity or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject.

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All features described herein in the context of "methods of the invention" apply equally to petrelintide for use according to the invention and the use according to the invention of petrelintide in preparation of a medicament.

15 ***Obesity and diseases associated with obesity***

The terms "disease", "disorder" and "condition" are synonymous and are used interchangeably herein to refer to a state of malfunction of the body. The term "disease" thus encompasses "disorder" and "condition".

20 The term "obesity" may be used herein to refer to overweight, obesity and morbid obesity together.

Petrelintide for use in the methods and medical uses of the present invention reduces body fat or prevent increase in body fat or inhibit gain of body fat whilst preserving lean mass.

25 Petrelintide may therefore provide an attractive treatment option for, *inter alia*, obesity and metabolic diseases caused, characterised by, or associated with, excess body weight.

Accordingly, the invention provides methods and medical uses of treating or preventing overweight, obesity, morbid obesity or a disease associated with overweight, obesity or morbid obesity in a subject.

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In some embodiments, the methods of the invention is a method of treating or preventing a disease associated with overweight, obesity or morbid obesity.

In some embodiments, the methods of the invention is a method of treating a disease associated with overweight, obesity or morbid obesity.

35

In some embodiments, the methods of the invention is a method preventing a disease associated with overweight, obesity or morbid obesity.

A disease associated with overweight, obesity or morbid obesity may also be referred to herein as a disease associated with obesity or morbid obesity.

Thus, in some embodiments, the methods of the invention is a method of treating or

5 preventing a disease associated with obesity or morbid obesity.

In some embodiments, the methods of the invention is a method of treating a disease associated with obesity or morbid obesity.

In some embodiments, the methods of the invention is a method preventing a disease associated with obesity or morbid obesity.

10

In some embodiments, the disease associated with overweight, obesity or morbid obesity is selected from the group consisting of hypertension, dyslipidemia, sleep apnea, cardiovascular disease, binge-eating disorder, Prader-Willi syndrome, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease, respiratory
15 problems, degeneration of cartilage, osteoarthritis, reproductive health complications such as infertility, Alzheimer's disease, diabetes, pre-diabetes, insulin resistance syndrome, impaired glucose tolerance (IGT), disease states associated with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, atherogenic dyslipidemia, hepatic steatosis ("fatty liver"), kidney failure, arteriosclerosis, macrovascular
20 disease, microvascular disease, diabetic heart disease, coronary heart disease, peripheral artery disease or stroke, and combinations thereof.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is hypertension.

25 In some embodiments, the disease associated with overweight, obesity or morbid obesity is dyslipidemia.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is sleep apnea.

30 In some embodiments, the disease associated with overweight, obesity or morbid obesity is cardiovascular disease.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is binge-eating disorder.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is Prader-Willi syndrome.

35 In some embodiments, the disease associated with overweight, obesity or morbid obesity is obesity prior to surgery.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is obesity-linked inflammation.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is obesity-linked gallbladder disease.

- 5 In some embodiments, the disease associated with overweight, obesity or morbid obesity is respiratory problems.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is degeneration of cartilage.

- 10 In some embodiments, the disease associated with overweight, obesity or morbid obesity is osteoarthritis.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is reproductive health complications. In some embodiments, the disease associated with overweight, obesity or morbid obesity is infertility.

- 15 In some embodiments, the disease associated with overweight, obesity or morbid obesity is Alzheimer's disease.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is diabetes. In some embodiments, the diabetes is type 1 diabetes. In some embodiments, the diabetes is type 2 diabetes.

- 20 In some embodiments, the disease associated with overweight, obesity or morbid obesity is pre-diabetes.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is insulin resistance syndrome.

- 25 In some embodiments, the disease associated with overweight, obesity or morbid obesity is impaired glucose tolerance (IGT).

In some embodiments, the disease associated with overweight, obesity or morbid obesity is a disease state associated with elevated blood glucose levels

- 30 In some embodiments, the disease associated with overweight, obesity or morbid obesity is metabolic disease. In some embodiments, the disease associated with overweight, obesity or morbid obesity is metabolic syndrome.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is hyperglycemia.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is atherogenic dyslipidemia.

- 35 In some embodiments, the disease associated with overweight, obesity or morbid obesity is hepatic steatosis ("fatty liver"). In some embodiments, the hepatic steatosis is non-alcoholic

fatty liver disease (NAFLD). In some embodiments, the NAFLD is non-alcoholic steatohepatitis (NASH).

In some embodiments, the hepatic steatosis is Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). In some embodiments, the hepatic steatosis is Metabolic

- 5 (dysfunction) associated fatty liver disease (MAFLD). In some embodiments, the hepatic steatosis is Metabolic dysfunction-associated steatohepatitis (MASH).

In some embodiments, the disease associated with overweight, obesity or morbid obesity is kidney failure.

- 10 In some embodiments, the disease associated with overweight, obesity or morbid obesity is arteriosclerosis. In some embodiments, the arteriosclerosis is atherosclerosis.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is macrovascular disease.

- 15 In some embodiments, the disease associated with overweight, obesity or morbid obesity is microvascular disease.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is diabetic heart disease. In some embodiments, the diabetic heart disease is diabetic cardiomyopathy. In some embodiments, the diabetic heart disease is heart failure as a diabetic complication.

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In some embodiments, the disease associated with overweight, obesity or morbid obesity is coronary heart disease.

In some embodiments, the disease associated with overweight, obesity or morbid obesity is peripheral artery disease.

- 25 In some embodiments, the disease associated with overweight, obesity or morbid obesity is stroke.

The invention also provides methods and medical uses of reducing body fat whilst

preserving lean mass in a subject, wherein the subject suffers from a disease. In such

- 30 embodiments of the invention, the reduction of body fat whilst preserving lean mass treats or prevents the disease.

The invention also provides methods and medical uses of inhibiting weight gain whilst

preserving lean mass in a subject, wherein the subject suffers from a disease. In such

- 35 embodiments of the invention, the inhibition of weight gain whilst preserving lean mass treats or prevents the disease.

In some embodiments, the subject suffers from a disease selected from the group consisting of hypertension, dyslipidemia, sleep apnea, cardiovascular disease, binge-eating disorder, Prader-Willi syndrome, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease, respiratory problems, degeneration of cartilage, osteoarthritis,

- 5 reproductive health complications such as infertility, Alzheimer's disease, diabetes, pre-diabetes, insulin resistance syndrome, impaired glucose tolerance (IGT), disease states associated with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, atherogenic dyslipidemia, hepatic steatosis ("fatty liver"), kidney failure, arteriosclerosis, macrovascular disease, microvascular disease, diabetic heart
- 10 disease, coronary heart disease, peripheral artery disease or stroke, and combinations thereof. The reduction of body fat, inhibition of weight gain or inhibition of gain of body fat whilst preserving lean mass treats or prevents the disease(s).

The diabetes may be type 1 diabetes or type 2 diabetes.

- 15 The arteriosclerosis may be atherosclerosis.

The hepatic steatosis may be non-alcoholic fatty liver disease (NAFLD). The NAFLD may which be non-alcoholic steatohepatitis (NASH).

In some embodiments, the hepatic steatosis is Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). In some embodiments, the hepatic steatosis is Metabolic

- 20 (dysfunction) associated fatty liver disease (MAFLD). In some embodiments, the hepatic steatosis is metabolic dysfunction-associated steatohepatitis (MASH).

The diabetic heart diseases may be diabetic cardiomyopathy or heart failure as a diabetic complication.

25

Petrelintide is useful, inter alia, in the reduction of food intake, promotion of weight loss, and inhibition or reduction of weight gain. Thus, petrelintide may be used in methods of treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess body weight.

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Petrelintide may also be used to lower circulating LDL levels and/or increase HDL/LDL ratio.

In some embodiments, the subject suffers from metabolic syndrome. Metabolic syndrome is characterized by a group of metabolic risk factors in one person. They include abdominal

35 obesity (excessive fat tissue around the abdominal internal organs), atherogenic dyslipidemia (blood fat disorders including high triglycerides, low HDL cholesterol and/or high LDL cholesterol, which foster plaque buildup in artery walls), elevated blood pressure

(hypertension), insulin resistance and glucose intolerance, prothrombotic state (e.g. high fibrinogen or plasminogen activator inhibitor–1 in the blood), and proinflammatory state (e.g., elevated C-reactive protein in the blood). Individuals with metabolic syndrome are at increased risk of coronary heart disease and other diseases related to other manifestations of arteriosclerosis (e.g. stroke and peripheral vascular disease). The dominant underlying risk factor for this syndrome appears to be abdominal obesity.

In some embodiments, the subject has diabetes. In some embodiments, the subject has a disease linked to obesity or to diabetes. In some embodiments, the disease is overweight. In some embodiments, the disease is obesity. In some embodiments, the disease is morbid obesity. In some embodiments, the disease is diabetes. In some embodiments, the disease is type 1 diabetes. In some embodiments, the disease is type 2 diabetes. In some embodiments, the disease is a disease linked to obesity or to diabetes.

Effects of petrelintide on these conditions may be mediated in whole or in part via an effect on body weight, or may be independent thereof. Treatment may be achieved, for example, by control of appetite, feeding, food intake, calorie intake and/or energy expenditure.

Diseases associated with gain of body fat and loss of lean mass

In some embodiments of the methods and medical uses of the invention, the subject suffers from a disease associated with weight gain. A disease associated with weight gain is a disease wherein the body weight of the subject increases or is at risk of increasing due to the disease. Typically, the increase in body weight is due to an increase in body fat. In some embodiments, the subject suffers from a disease associated with gain of body fat or increase in body fat.

In some embodiments of the methods and medical uses of the invention, the subject suffers from a disease associated with loss of lean mass. A disease associated with loss of lean mass is a disease wherein the lean mass of the subject decreases or is at risk of decreasing due to the disease. Typically, loss of lean mass is specifically loss of muscle (i.e. loss of muscle mass, also referred to as muscle wasting). In some embodiments, the subject suffers from a disease associated with loss of muscle mass. In some embodiments, the subject suffers from a disease associated with muscle wasting or atrophy (i.e. a disease wherein the muscle mass of the subject decreases or is at risk of decreasing due to the disease).

In some embodiments, the subject suffers from a disease associated with both gain of body fat and loss of lean mass.

Diseases associated with both gain of body fat and loss of lean mass are often diseases associated with exercise intolerance. A disease associated with exercise intolerance is a disease wherein the subject suffering from the disease finds it difficult to exercise.

- 5 Consequently, the subject is at risk gain of body fat and loss of lean mass (i.e. loss of muscle mass, muscle wasting).

- Diseases associated with both gain of body fat and loss of lean mass include sarcopenic obesity, Duchenne muscular dystrophy (DMD), Charcot-Marie-Tooth disease (CMT), chronic
10 obstructive pulmonary disease (COPD), McArdle disease, hypothyroidism, testosterone deficiency syndrome (TD), heart failure and anaemia.

- Thus, in some embodiments, the subject suffers from a disease selected from sarcopenic obesity, Duchenne muscular dystrophy (DMD), Charcot-Marie-Tooth disease (CMT), chronic
15 obstructive pulmonary disease (COPD), McArdle disease, hypothyroidism, testosterone deficiency syndrome (TD), heart failure and anaemia.

- Furthermore, the invention provides a method of treating or preventing sarcopenic obesity, Duchenne muscular dystrophy (DMD), Charcot-Marie-Tooth disease (CMT), chronic
20 obstructive pulmonary disease (COPD), McArdle disease, hypothyroidism, testosterone deficiency syndrome (TD), heart failure and anaemia in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

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- The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from sarcopenic obesity, Duchenne muscular dystrophy (DMD), Charcot-Marie-Tooth disease (CMT), chronic obstructive pulmonary disease (COPD), McArdle disease, hypothyroidism, testosterone deficiency syndrome (TD), heart
30 failure or anaemia, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

- The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from sarcopenic obesity, Duchenne muscular
35 dystrophy (DMD), Charcot-Marie-Tooth disease (CMT), chronic obstructive pulmonary disease (COPD), McArdle disease, hypothyroidism, testosterone deficiency syndrome (TD),

heart failure or anaemia, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

5 Sarcopenic obesity is a form of obesity characterised by coexistence of obesity (excess fat mass) and sarcopenia (low skeletal muscle mass and function). Sarcopenic obesity may be considered a general obesity related disease in view of obesity-linked muscle atrophy due to lack of exercise.

10 The invention provides a method of treating or preventing sarcopenic obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

15 The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from sarcopenic obesity, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

20 The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from sarcopenic obesity, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

25 Duchenne muscular dystrophy (DMD) is a severe X-linked paediatric neuromuscular disorder which is well known to cause muscle atrophy. Young people with DMD also have high rates of obesity. This is likely due to the disease itself and that a common treatment for DMD is steroid treatment, which is known to cause weight gain.

30 The invention provides a method of treating or preventing Duchenne muscular dystrophy (DMD) in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

35 The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from Duchenne muscular dystrophy (DMD), the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from Duchenne muscular dystrophy (DMD), the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Charcot-Marie-Tooth disease (CMT) is a condition that affects the peripheral nerves that control muscle movement. One symptom of CMT is muscle atrophy. CMT is also linked to children being overweight.

The invention provides a method of treating or preventing Charcot-Marie-Tooth disease (CMT) in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from Charcot-Marie-Tooth disease (CMT), the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from Charcot-Marie-Tooth disease (CMT), the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Chronic obstructive pulmonary disease (COPD) is a term used to describe chronic lung diseases including emphysema, and chronic bronchitis. This disease is characterized by breathlessness. Some people with COPD also experience tiredness and chronic cough with or without mucus. Approximately 65% of the COPD population is overweight or obese.

Patients with COPD also suffer from exercise intolerance and muscle wasting. Lean tissue depletion can occur in overweight patients.

The invention provides a method of treating or preventing Chronic obstructive pulmonary disease (COPD) in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from Chronic obstructive pulmonary disease (COPD), the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

5

The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from chronic obstructive pulmonary disease (COPD), the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

10

McArdle disease is a genetic disorder that effectively prevents exercise in patients; patients lack myophosphorylase which is an enzyme required to break down glycogen into glucose. This causes muscle pain and cramps during exercise.

15 McArdle disease often presents with muscle wasting. McArdle disease patients also have higher body fat & greater risk of suffering obesity.

The invention provides a method of treating or preventing McArdle disease in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method
20 comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from McArdle disease, the method comprising
25 administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from McArdle disease, the method comprising
30 administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Hypothyroidism (i.e. an underactive thyroid that does not produce enough thyroid hormone) is commonly associated with weight gain and may higher risk of obesity. Another symptom
35 of hypothyroidism is hypothyroid myopathy which is associated with muscle atrophy, in particular type 2 muscle fibre atrophy.

The invention provides a method of treating or preventing hypothyroidism in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject an amylin analogue or a pharmaceutically acceptable salt or solvate thereof, wherein the amylin analogue is petrelintide.

5

The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from hyperthyroidism, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

10

The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from hypothyroidism, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

15

Testosterone deficiency syndrome (TD) is associated with obesity and a loss of lean muscle mass.

The invention provides a method of treating or preventing testosterone deficiency syndrome (TD) in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject an amylin analogue or a pharmaceutically acceptable salt or solvate thereof, wherein the amylin analogue is petrelintide.

25 The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from testosterone deficiency syndrome, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

30 The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from testosterone deficiency syndrome (TD), the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

35 Heart failure results in exercise intolerance & thus contributes to both obesity and muscle atrophy / loss in skeletal muscle mass.

The invention provides a method of treating or preventing heart failure in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

5

The invention provides a method of reducing body fat whilst preserving lean mass in a subject, wherein the subject suffers from heart failure, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

10 The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from heart failure, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

15 Anaemia is iron deficiency or reduced haemoglobin concentration in the blood, which can lead to a reduction in the oxygen carrying capacity of the blood. In severe cases, this may cause exercise intolerance, and thus muscle wasting and obesity.

The invention provides a method of treating or preventing anaemia in a subject, wherein the
20 method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention provides a method of reducing body fat whilst preserving lean mass in a
25 subject, wherein the subject suffers from anaemia, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

The invention also provides a method of inhibiting weight gain whilst preserving lean mass in a subject, wherein the subject suffers from anaemia, the method comprising administering to
30 the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.

Weight loss dietary regime

In some embodiments of the methods and uses of the invention, the subject is following a dietary regimen.

35

A "dietary regimen" refers to a course of food to which the subject is restricted (a "diet" in colloquial terms, i.e., the subject is on a diet).

In some embodiments, the dietary regimen is a weight loss dietary regimen, which means a dietary regimen designed to induce weight loss. In some embodiments, the dietary regimen is one wherein the consumption of high-fat food is restricted (i.e. it is intended that the
5 subject does not consume high-fat food).

In other words, the invention encompasses combining treatment with petrelintide as described herein with a dietary regimen. Such a combination may be particularly effective in promoting weight loss (or avoiding weight gain) as petrelintide assists adherence to the
10 dietary regimen by causing the subject to prefer non-high-fat food.

Administration of petrelintide

“Administering” petrelintide to the subject means providing petrelintide to the subject such that petrelintide will have its physiological effect. Petrelintide may be administered to the
15 subject in any suitable manner or by any suitable means known in the art.

The term “administration event” is used herein to refer to a single act of administering petrelintide to the subject (which may be one of many such administration events).

20 Dose

The term “dose” refers to the quantity of petrelintide administered to a subject at each administration event. The term “dosage” refers to both the quantity and frequency at which a given compound is administered to a subject.

Petrelintide is administered to the subject in a therapeutically effective amount (i.e. a therapeutically effective dose). The term “therapeutically effective amount” as used herein refers to an amount that is sufficient to cure, ameliorate, alleviate or partially arrest the clinical manifestations of the particular disease, disorder or condition that is the object of the treatment or other therapeutic intervention in question e.g. as measured by established
25 clinical endpoints or other biomarkers (established or experimental). A therapeutically relevant amount may be determined empirically by one skilled in the art based on the indication being treated or prevented and the subject to whom the therapeutically relevant amount is being administered. For example, the skilled worker may measure one or more of the clinically relevant indicators of bioactivity described herein, e.g. plasma lipid levels, blood
30 glucose levels or insulin release. The skilled worker may determine a clinically relevant amount through *in vitro* or *in vivo* measurements. Other exemplary measures include weight gain, weight loss, and change in blood pressure.

An amount adequate to accomplish any or all of these effects is defined as a therapeutically effective amount. The administered amount and the method of administration can be tailored to achieve optimal efficacy. An amount effective for a given purpose will depend, *inter alia*,
5 on the severity of the disease, disorder or condition that is the object of the particular treatment or other therapeutic intervention, on the body weight and general condition of the subject in question, on diet, on possible concurrent medication, and on other factors well known to those skilled in the medical arts. Determination of an appropriate dosage size and dosing regimen most appropriate for administration of a peptide or pharmaceutically
10 acceptable salt or solvate thereof according to the invention to a human may be guided by the results obtained by the present invention, and may be confirmed in properly designed clinical trials. An effective dosage and treatment protocol may be determined by conventional means, starting with a low dose in laboratory animals and then increasing the dosage while monitoring the effects, and systematically varying the dosage regimen as well.
15 Numerous factors may be taken into consideration by a clinician when determining an optimal dosage for a given subject. Such considerations are well known to the skilled person.

The dose of petrelintide may be independently selected at each administration event.
20

In some embodiments, petrelintide is administered to the subject at a dose of about 0.0001 to about 100 mg/kg body weight per day, such as about 0.0005 to about 50 mg/kg body weight per day, such as about 0.001 to about 10 mg/kg body weight per day, such as about 0.01 to about 1 mg/kg body weight per day.
25

In some embodiments, petrelintide is administered to the subject at a dose of about 0.0007 to about 700 mg/kg body weight per week, such as about 0.0035 to about 350 mg/kg body weight per week, such as about 0.007 to about 70 mg/kg body weight per week.

30 In some embodiments, petrelintide is administered to the subject at a dose of about 0.05 to about 50,000 mg per week, such as about 0.25 to about 25,000 mg per week, such as about 0.5 to about 5,000 mg per week.

In some embodiments, the weekly dose is more than 2.4 mg up to 10.0 mg. In other words,
35 in some embodiments, the weekly dose is higher than 2.4 mg, up to at most 10.0 mg. In some embodiments, the dose is more than 3.6 mg up to 10.0 mg, more than 4.0 mg up to

10.0 mg, more than 4.8 mg up to 10.0 mg, more than 6.0 mg up to 10.0 mg, or more than 7.5 mg up to 10.0 mg.

In some embodiments, petrelintide is administered to the subject at a dose of about 2 nmol/kg body weight or about 10 nmol/kg body weight.

5

Timing of administration

Petrelintide may be administered to the subject a certain number of times “daily” or a certain number of times “a day”. “A day” is intended to mean approximately 24 hours, for example, approximately 20, 21, 22, 23, 24, 25, 26, 27 or 28 hours.

10

In some embodiments, reference to “day” may mean 24 hours $\pm$ 8 hours. That is to say the administration may take place either up to and including about eight hours before, or up to and including about eight hours after the stated time.

15 Petrelintide may be administered to the subject a certain number of times “weekly” a certain number of times “a week”. A “week” is intended to mean approximately 7 days, for example, approximately 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 or 9 days with each “day” being counted as approximately a 24 hour period.

20 In some embodiments, reference to “week” may mean 7 days $\pm$ 2 days. That is to say the administration may take place either up to and including about two days before, or up to and including about two days after the stated day. As such, the administration may take place about 2 days or about 1 day before, or about 1 day or about 2 days after, the stated day. Hence, the administration may take place 2 days or 1 day before, or 1 day or 2 days after,
25 the stated day.

In some embodiments, petrelintide is administered to the subject once daily, twice daily, once every two, three, four, five or six days, once weekly, twice weekly, once monthly or twice monthly. In some embodiments is administered to the subject once or twice weekly.

30 Preferably, petrelintide is administered to the subject once weekly.

In some embodiments, petrelintide is administered to the subject twice daily, once every two days or once every four days.

35 As will be appreciated in the art, the time between doses may be varied to some extent so that each and every dose is not separated by precisely the same time (i.e. not precisely a

day or precisely a week). This will often be directed under the discretion of the physician. Thus, doses may be separated in time by a clinically acceptable range of times.

Route of administration

- 5 The administration to a subject of petrelintide described herein may be by any mode of administration common or standard in the art. In some embodiments, petrelintide is administered to the subject by injection, such as by subcutaneous (sc), intramuscular (im) or intravenous (iv) injection. In preferred embodiments, administration is by subcutaneous injection. Preferably, petrelintide is in a form suitable for subcutaneous (s/c or s.c.)
10 administration to a subject.

Administration period

- The term "administration period" may be used herein to refer to the total period in which petrelintide is administered to the subject. In other words, the administration period is the
15 period starting with the first administration event (i.e. the first time the compound is administered to the subject) and ending with the final administration event (i.e. the final time the compound is administered to the subject). Alternatively expressed, the administration period is the period in which subject is treated with the compound.
- 20 In some embodiments, petrelintide is administered to the subject for at least one month (i.e. the administration period for the amylin analogue is at least one month). In some embodiments, petrelintide is administered to the subject for at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven
25 months, or at least twelve months.

- In some embodiments, petrelintide is administered to the subject for at least one year (i.e. the administration period for the amylin analogue is at least one year). In some
embodiments, petrelintide is administered to the subject for at least two years, at least three
30 years, at least four years, at least five years, at least six years, at least seven years, at least eight years, at least nine years, or at least ten years.

- Petrelintide is a chronic treatment. In some embodiments, petrelintide is administered to the subject for more than ten years. In some embodiments, petrelintide is administered to the
35 subject indefinitely. In some embodiments, petrelintide is administered to the subject for the rest of the subject's life.

Pharmaceutical compositions

Petrelintide as described herein may be formulated as a pharmaceutical composition. The terms “pharmaceutical composition”, “composition” and “formulation” are used interchangeably herein. As with all aspects of the invention, it is to be understood that
5 reference to petrelintide encompasses reference to pharmaceutically acceptable salts and solvates.

Thus, the invention also provides a methods as described herein comprising administering to a subject a pharmaceutical composition comprising petrelintide as described herein or a
10 pharmaceutically acceptable salt or solvate thereof.

The invention also provides a pharmaceutical composition comprising petrelintide as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in a method as described herein.

15 In some embodiments, the composition comprises a pharmaceutically acceptable carrier, excipient or vehicle.

Petrelintide may be formulated as a pharmaceutical composition which is suited for
20 administration with or without storage, and which typically comprises a therapeutically effective amount of petrelintide, together with a pharmaceutically acceptable carrier, excipient or vehicle.

The term “pharmaceutically acceptable carrier” includes any of the standard pharmaceutical
25 carriers. Pharmaceutically acceptable carriers for therapeutic use are well known in the pharmaceutical art and are described, for example, in “Remington's Pharmaceutical Sciences”, 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985. For example, sterile saline and phosphate-buffered saline at slightly acidic or physiological pH may be used. Suitable pH-buffering agents may, e.g., be phosphate,
30 citrate, acetate, tris(hydroxymethyl)aminomethane (TRIS), N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid (TAPS), ammonium bicarbonate, diethanolamine, histidine, arginine, lysine or acetate (e.g. as sodium acetate), or mixtures thereof. The term further encompasses any carrier agents listed in the US Pharmacopeia for use in animals, including humans.

35 In some embodiments, the pharmaceutical composition is a stable aqueous liquid pharmaceutical composition (i.e. a stable aqueous liquid formulation).

Preferably the formulations of the present invention substantially do not include organic solvent. In particular preferred embodiments, water is the sole solvent used to make the aqueous liquid formulation.

5

The formulations of the invention are aqueous liquid formulations, i.e. formulations comprising water, in the form of an aqueous solution. In the context of the invention the term "aqueous formulation" will normally refer to a formulation comprising at least 50 % by weight (50 % w/w) of water as a solvent, more preferably at least 75% w/w of water, more

10 preferably at least 80% w/w of water, more preferably at least 85% w/w of water, more preferably at least 90% w/w of water, most preferably at least 95% w/w of water. In certain embodiments, aqueous formulations of the present invention substantially do not include organic solvents, such as aprotic polar solvents such as dimethyl sulfoxide (DMSO). "Substantially" in this sense means that the aqueous formulations include less than 5% by
15 volume organic solvent, more preferably less than 2% by volume (v/v) organic solvent and even more preferably less than 1% by volume (v/v) organic solvent. In preferred embodiments, no organic solvent is present. Thus, typically, water is the sole solvent used to make the aqueous liquid formulations.

20 ***Petrelintide concentration***

In some embodiments, petrelintide is present in the composition at a concentration of from about 0.4 mg/ml to about 25 mg/ml.

In some embodiments, petrelintide is present in the composition at a concentration of at
25 least about 0.4 mg/ml, at least about 0.5 mg/ml, at least about 0.6 mg/ml, at least about 1.2 mg/ml, or at least about 2.5 mg/ml.

In some embodiments, petrelintide is present in the composition at a concentration of up to
30 about 25 mg/ml, up to about 20 mg/ml, up to about 15 mg/ml, or up to about 10 mg/ml.

In some embodiments, petrelintide is present in the composition at a concentration of about 3 mg/ml to about 12 mg/ml, e.g. about 3 mg/ml to about 7 mg/ml or about 8 mg/ml to about 12 mg/ml, e.g. about 5 mg/ml or about 10 mg/ml.

Buffer

The term "buffer" as used herein denotes a pharmaceutically acceptable agent which stabilizes the pH of a pharmaceutical formulation. Suitable buffers are well known in the art and can be found in the literature.

5

Any suitable buffer may be used, including a phosphate buffer, histidine buffer, TRIS (tris(hydroxymethyl)aminomethane) buffer, acetate buffer, arginine buffer, citrate buffer, bicarbonate buffer, diethanolamine buffer, lysine buffer and TAPS ([tris(hydroxymethyl)methylamino]propanesulfonic acid) buffer. Particularly preferred buffers include phosphate buffer, histidine buffer, citrate buffer and TRIS buffer, especially phosphate buffer, histidine buffer and citrate buffer.

10

In some embodiments, the buffer is present at a concentration of about 0.5 mM to about 25 mM.

15

In some embodiments, the buffer is present at a concentration of about 0.5 mM to about 20 mM, about 0.5 mM to about 15 mM, about 1 mM to about 15 mM, about 1 mM to about 12 mM, about 3 mM to about 7 mM, about 8 mM to about 12 mM, or about 5 mM or about 10 mM, e.g. about 5 mM or about 10 mM particularly (but not exclusively) when the buffer is phosphate, histidine or citrate.

20

In some embodiments, the buffer is phosphate, histidine or citrate.

For TRIS buffer, it may be preferred to be present at about 15 mM to about 25 mM, e.g. about 17 mM to about 23 mM, e.g. about 20 mM, since the buffering capacity of TRIS is lower than that of other buffers such as (e.g.) phosphate and histidine in the relevant pH range.

25

It may be possible for the formulation to contain more than one buffer, e.g. two buffers, or even more. In such cases, the quoted concentration may represent the sum of the concentrations of the individual buffers. For example, a formulation containing 2.5 mM phosphate buffer and 2.5 mM histidine buffer may be considered to contain 5 mM buffer overall.

30

pH

35

The pH of the formulation was also found to be significant for stability. Chemical stability was increased at lower pH values and physical stability was maintained. Thus, in some

embodiments, the formulation has a pH of about 5.8 to about 6.9, and may, for example, have a pH of about 6.2 to about 6.8, e.g. about 6.4 to about 6.6, e.g. about 6.5. For the avoidance of doubt, pH is measured at 25°C.

5 ***Tonicity modifier***

In some embodiments, the composition comprises a tonicity modifier.

The term "tonicity modifier" as used herein denotes pharmaceutically acceptable tonicity agents that are used to modulate the tonicity of the formulation. The terms "tonicity modifier" and "tonicity agent" may be used interchangeably. The formulations of the present invention are preferably isosmotic, that is they have an osmotic pressure that is substantially the same as human blood serum, e.g. about 300+/-80 mOsm, e.g. 300+/-60 mOsm, as measured by an osmometer.

The tonicity modifier may be ionic or non-ionic. Suitable ionic tonicity modifiers include alkali metal salts (e.g. halides) and earth metal salts (e.g. halides), such as NaCl, NaBr, NaI, KCl, KBr, KI, LiCl, CaCl₂ and Na₂SO₄. Non-ionic tonicity modifiers include mannitol (e.g. D-mannitol), propylene glycol, sucrose, glycerol, sorbitol and trehalose. In some embodiments, mannitol (e.g. D-mannitol), propylene glycol and NaCl may be preferred as tonicity modifiers, especially mannitol and propylene glycol.

Where the tonicity modifier is a chloride salt, such as NaCl, it may be desirable that the tonicity modifier is only added to the formulation once the pH has been adjusted to the desired value. This may particularly be the case where petrelintide is itself provided in the form of a chloride salt, since the presence of chloride ions above a certain level may promote precipitation or fibrillation of the amylin analogue at pH values around the pI of the peptide (pI = 4.36).

It will be understood that the concentration of the tonicity modifier will be dependent on the concentration of other components of the formulation, especially where the formulation is intended to be isosmotic. The skilled person is capable of establishing the appropriate concentration for any given agent, in the context of a specific formulation.

For example, it may be appropriate to employ mannitol in a concentration of 200–300 mM, e.g. 230-260 mM; it may be appropriate to employ propylene glycol in a concentration of 200-250 mM, e.g. 224 mM; it may be appropriate to employ NaCl in a concentration of 100-150mM, e.g. 118-137mM.

Preservative

In some embodiments, the composition comprises a preservative, especially when it is provided in a multi-use format. Alternatively, and especially when provided in single-use
5 format, the formulation may contain no or substantially no preservative. When a preservative is present, it will be employed in an amount effective to kill a range of bacterial types as required for regulatory approval. Suitable preservatives include meta-cresol, phenol, methylparaben, ethylparaben, propylparaben, butylparaben, chlorobutanol, benzyl alcohol, phenylmercuric nitrate, thimerosal, sorbic acid, potassium sorbate, benzoic acid,
10 chlorocresol and benzalkonium chloride. The preservative will be present in an amount effective to kill a range of bacterial types as required for regulatory approval.

Stability

The aqueous liquid formulation is typically stable for at least 6 months, e.g. at least 12
15 months, at least 18 months or at least 24 months, at 2-8°C (e.g. at 5°C). Preferably it is stable for at least 18 months, e.g. at least 24 months, at 2-8°C (e.g. at 5°C).

For example, the formulation may display substantially no changes indicative of reduced physical stability (e.g. as demonstrated by turbidity of the solution, or of aggregation,
20 fibrillation or gelling of petrelintide) after it has been stored at 2-8°C (e.g. at 5°C) for at least 6 months, at least 12 months, at least 18 months, or at least 24 months. Preferably, the formulation displays substantially no such changes after it has been stored at 2-8°C (e.g. at 5°C) for at least 18 months, e.g. at least 24 months. It will be understood that accelerated conditions may also be employed as a proxy for assessing longer term physical stability as
25 set out in more detail below.

Additionally, or alternatively, at least 80%, more preferably at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of the petrelintide remains in intact monomeric form in the formulation after it has been stored at 2-8°C (e.g. at
30 5°C) for at least 6 months, at least 12 months, at least 18 months, or at least 24 months. Preferably, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of the petrelintide remains in intact monomeric form after it has been stored at 2-8°C (e.g. at 5°C) for at least 6 months, at least 12 months, at least 18 months, or at least 24 months. More preferably, at least 90%, at least 95%, at least 96%, at least 97%, at least
35 98%, or at least 99% of the petrelintide remains in intact monomeric form in the formulation after it has been stored at 2-8°C (e.g. at 5°C) for at least 18 months, e.g. at least 24 months.

Further aspects of the compositions

In these formulations, as elsewhere, petrelintide is provided as a chloride salt, e.g. having the formula:

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

5 Hyp-NH₂), x(Cl)

where x is 1.0-2.0.

In accordance with normal pharmaceutical practice, the formulations of the present invention are sterile and/or free (or substantially free, e.g. containing no more than about 100 ppm) of
10 reducing agent.

The formulations are suitable for parenteral administration, typically by injection. Thus administration may, for example, be by subcutaneous, intramuscular, intraperitoneal or intravenous injection, although subcutaneous administration may be preferred.

15

An individual dose of a formulation of the invention may be provided in any suitable volume. For example, an individual dose may have a volume of 0.1 to 1.5 ml, for example 0.3 to 1.5 ml, for example 0.3 ml to 1 ml. Examples of specific individual dose volumes include 0.5 ml and 1 ml (e.g. 1.0 ml). Individual doses may be packaged separately for single use, e.g. in
20 individual vials, cartridges or syringes, as described in more detail below.

The formulations of the invention may be provided in a container or delivery device. In some embodiments, the container or delivery device is for single use. In other embodiments, the container or delivery device is for multi-use.

25

Examples include a sealed vial, a pre-filled syringe, and an injector device such as an injector pen, an adjustable dose auto-injector, a disposable auto-injector, a wearable injector, or an infusion pump.

30 A pharmaceutical composition of the invention may be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component or components.

In some embodiments, the pharmaceutical composition is as follows:

Component	Quantity/mL Drug product	Function
petrelintide	4.0 mg	Active pharmaceutical ingredient

Trometamol/Tromethamine (TRIS)	2.42 mg	Buffer
Sodium chloride	6.9 mg	Tonicity agent
1M Hydrochloric acid	q.s.	pH adjustment
0.5 M Sodium hydroxide	q.s.	pH adjustment
Water for injection	Ad 1.0 mL	Solvent

Sequence listing

- SEQ ID NO: 1 – Petrelintide
- SEQ ID NO: 2 – Native human amylin
- 5 SEQ ID NO: 3 – Liraglutide

EXAMPLES

The following examples are provided to illustrate preferred aspects of the invention and are not intended to limit the scope of the invention.

10

Example 1: Effect of peptides on body composition in obese rats

This study was performed to assess the effect of treatment with peptides on body composition (i.e. effect on loss of body fat and loss of lean mass) in diet-induced obese (DIO) rats.

15

Briefly, DIO rats were generated by feeding them a high-fat diet for 21 weeks. Then, over the course of a 30-day study period, the rats were administered vehicle (as negative control) or one of petrelintide or liraglutide.

20

Liraglutide, which is a derivative of GLP-1 described in Example 37 of US patent no. 6,268,343, has the formula:

Hy-HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG-OH (SEQ ID NO: 3),
wherein the side-chain amino group of the lysine at position 20 is linked to the lipophilic moiety hexadecanoyl (i.e. palmitoyl) via a γ-Glu linker.

25

Body weight of the rats was measured daily throughout the study period. Body fat and lean mass of the rats were measured using EchoMRI close to the end of the study period (day 29).

30

Rats administered petrelintide or liraglutide are referred the as “treatment groups” herein (in contrast to the vehicle group used as control).

Administration

Vehicle was administered once every 2 days (Q2D).

- Petrelintide was administered at both a lower dose (2 nmol/kg body weight) and a higher
 5 dose (10 nmol/kg body weight). The lower dose of petrelintide was administered once every 2 days (Q2D). The higher dose of petrelintide was administered once every 4 days (Q4D).

Liraglutide was administered twice daily (BID).

- 10 In these Examples, "Q2D" means administration once every 2 days, "Q4D" means administration once every 4 days and "BID" means administration twice every day.

Vehicle and peptides were all administered by subcutaneous injection (sc).

- 15 Petrelintide was formulated using 50mM histidine buffer pH 7.0 with 200 mM mannitol. For the vehicle group the same buffer without compound was used. Liraglutide was formulated using PBS with 0.1% bovine serum albumin.

The treatment groups for this study are summarised in Table 1 below:

20 **Table 1 – Study group summary**

Group name	Dose	Dosing frequency	Administration route
Vehicle	-	Once every 2 days	Subcutaneous injection (sc)
Petrelintide Q2D	2 nmol/kg / 0.0086 mg/kg	Once every 2 days	Subcutaneous injection (sc)
Petrelintide Q4D	10 nmol/kg / 0.0426 mg/kg	Once every 4 days	Subcutaneous injection (sc)
Liraglutide	5 nmol/kg / 0.02 mg/kg	Twice every day	Subcutaneous injection (sc)

Animal model

- Healthy male Sprague Dawley rats were obtained from Taconic (Denmark). The rats were 5 weeks of age at arrival. To generate DIO rats for the study, animals were fed with chow
 25 (cereal-based pellets – Altromin 1324, Brogaarden, Denmark) and high-fat diet (Gubra diet containing 60% of total energy) from fat ad libitum for 21 weeks. The Gubra diet is a highly palatable high-fat, high-sugar diet made up of a paste (1:1:1) of chocolate spread (Nutella, Ferrero, Italy), peanut butter (Skippy, Unilever, USA) and powdered regular rodent chow (Altromin 1324, Brogaarden, Denmark). Animals were housed in groups of 2, on a 12-hour
 30 light and 12-hour dark cycle (with lights on at 3am-3pm) at standard temperature and humidity conditions (19-23°C, 40-60% relative humidity) with ad libitum access to domestic

quality tap water. Animals were stratified based on EchoMRI scan (fat) and bodyweight on day -1.

Results

- 5 Body weight of each rat was measured at the same time every day throughout the 30-day study period. **Figure 1** shows the actual (A) and relative (B) body weight change (day 1 = 100%) over the study period.

- 10 Absolute body weight appeared to decrease for all three treatment groups relative to the vehicle-treated group during the study period, though the change was not statistically significantly.

- However, relative body weight decreased significantly during the study period in all three treatment groups: from day 3 and onwards in the petrelintide high dose group, and from day 15 7 and day 12 and onwards in the petrelintide low dose and the liraglutide groups, respectively.

- In particular, as shown in **Figure 2**, treatment with liraglutide and petrelintide resulted in significantly lower relative body weight compared to vehicle ($3.3 \% \pm 0.7$ vehicle, $-0.1 \% \pm 1.1$ liraglutide, $-4.1 \% \pm 0.6$ petrelintide 2 nmol/kg, $-7.8 \% \pm 0.7$ petrelintide 10 nmol/kg; relative to initial body weights $\pm$ SEM).
- 20

- The body fat composition of each rat was measured at day 29 of the study period by EchoMRI. **Figure 3** shows whole body fat composition in grams (g) (A) and whole body fat composition as percentage of body weight (%) (B) at the end of the study (day 29), and the difference in whole body fat composition (%) compared to the start of the study (terminal-baseline) (C).
- 25

- Treatment with petrelintide at both high and low dosages induced a significant decrease in relative whole body fat composition during the study as compared to the vehicle-treated group.
- 30

- In particular, treatment with petrelintide resulted in significant reduction of fat mass in comparison to vehicle, which liraglutide did not ($2.0 \% \pm 0.5$ liraglutide, $-0.3 \% \pm 0.5$ petrelintide 2 nmol/kg, $-1.6 \% \pm 0.5$ petrelintide 10 nmol/kg, $3.2 \% \pm 0.4$ vehicle; mean change in fat mass as % of body weight $\pm$ SEM) (**Figure 3C**).
- 35

The lean mass composition of each rat was measured at day 29 of the study period by EchoMRI. **Figure 4** shows whole body lean mass composition in grams (g) (A) and whole body lean mass composition as percentage of body weight (%) (B) at the end of the study (day 29), and the difference in whole body lean mass composition (%) compared to the start of the study (terminal-baseline) (C).

In particular, treatment with petrelintide resulted in significant preservation of relative lean mass in comparison to vehicle, which liraglutide did not ($-3.8 \% \pm 0.3$ vehicle, $-2.4 \% \pm 0.6$ liraglutide, $-0.8 \% \pm 0.4$ petrelintide 2 nmol/kg, $0.1 \% \pm 0.4$ petrelintide 10 nmol/kg; mean change in lean mass as % of body weight $\pm$ SEM).

Treatment with high dosage of petrelintide induced a significant increase in relative whole body lean mass composition. Thus, treatment with petrelintide resulted in reduced body fat whilst preserving lean mass.

Example 2: Effect of peptides on fat mass and muscle mass in obese rats

This study was performed to assess the effect of treatment with peptides on fat mass and muscle mass of specific fat depots and specific muscles (i.e. effect on loss of body fat and loss of muscle mass) in diet-induced obese (DIO) rats.

DIO rats were generated by feeding them a high-fat diet for 16 weeks. Then, over the course of a 21-day study period, the rats were administered vehicle (as negative control) or petrelintide as used in Example 1. Body weight of the rats was measured daily throughout the study period. Fat mass and muscle mass was assessed at termination by dissection of specific fat depots and muscles. Inguinal white adipose tissue was dissected and weighed as an example of subcutaneous fat and epididymal white adipose tissue was dissected and weighed as an example of visceral fat. From the hindleg the following muscles were dissected and weighed: gastrocnemius, soleus, tibialis, and extensor digitorum longus.

Administration

Vehicle and petrelintide was administered by subcutaneous injection (sc) once every 2 days (Q2D). Petrelintide was administered at a dose of 10nmol/kg.

The formulation used for each treatment (vehicle or petrelintide) was 20 mM Phosphate pH 7.5, 260 mM mannitol.

The treatment groups for this study are summarised in Table 2 below:

Table 2 – Study group summary

Group name	Dose	Dosing frequency	Administration route
Vehicle	-	Once every 2 days	Subcutaneous injection (sc)
Petrelintide	10 nmol/kg / 0.0426 mg/kg	Once every 2 days	Subcutaneous injection (sc)

Animal model

DIO male Sprague Dawley rats were obtained from Taconic (Denmark). The rats were 18 weeks of age at arrival. At 6 weeks of age the rats were switch to feed high-fat diet containing 60% of total energy from fat ad libitum for 12 weeks, while the animals were at Taconic. Animals were housed in groups of 2, on a 12-hour light and 12-hour dark cycle (with lights on at 6am-6pm) at standard temperature and humidity conditions (19-23°C, 40-60% relative humidity) with ad libitum access to domestic quality tap water. Animals were stratified based on bodyweight on day -11.

Results

Body weight of each rat was measured every day throughout the 21-day study period. **Figure 5** shows the actual (A) and relative (B) body weight change (day 1 = 0%) over the study period. Data is expressed as mean $\pm$ standard error of the mean (SEM) (n = 10). Absolute body weight and relative body weight change appeared to decrease for petrelintide treated animals relative to the vehicle-treated group during the study period, though it was only the relative body weight change that was statistically significantly.

The body fat was assessed by dissection and weighing of inguinal white adipose tissue and epididymal white adipose tissue at termination of the study. **Figure 6** shows that both inguinal fat (A) and epididymal fat (B) were significantly reduced by treatment with petrelintide compared to vehicle treatment.

The body muscle mass was assessed by dissection and weighing of four specific muscles (gastrocnemius, soleus, tibialis, and extensor digitorum longus) at termination of the study. **Figure 7** shows that there was no significant difference in muscle mass between vehicle treated animals and petrelintide treated animals gastrocnemius (A), soleus (B), tibialis (C), and extensor digitorum longus (D) muscles.

In summary, treatment with petrelintide induced a significant decrease in fat mass of both fat depots without any change in the four muscles dissected, when compared to vehicle treated animals.

These data demonstrate that treatment with petrelintide reduces body weight through reduction specifically of fat rather than muscle.

Example 3: Phase 1 clinical trial assessing multiple ascending doses

5 A multiple ascending dose (MAD) trial assessing safety, tolerability, pharmacokinetics, and pharmacodynamics of petrelintide administered to healthy participants was performed.

Participants were healthy male participants or female participants of non-childbearing potential that were overweight and obese, but otherwise healthy, with a Body Mass Index (BMI) between 27.0 and 39.9 kg/m².

Trial design

The MAD trial was a single-centre, randomised and double-blind within cohorts, placebo-controlled, sequential multiple ascending dose trial in overweight and obese, but otherwise healthy participants, randomised to petrelintide or placebo (randomisation ratio 3:1) within the cohort (1.0, 1.0, 2.0, 2.0, 4.0, 4.0, 6.0, 6.0, 7.5, 7.5 mg followed by a maintenance dose of 9.0 mg for 6 weeks).

16 participants, where subjects in a 3:1 ratio with 12 participants received petrelintide and 4 participants received placebo in the cohort.

The total observation period was 26 weeks started with an initial in-house stay (from Day -1 to Day 2), with scheduled discharge on Day 2, followed by 3 ambulatory visits for once-weekly dosing, and subsequent 13 in-house visits of 1-4 overnight stays depending on the dose level. The 16 once-weekly administrations (Day 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99 and 106) were followed by five ambulatory visits (Day 110, 113±1, 120±1, 134±1, 148±1) and an End of Trial (EOT) Visit on Day 176±2.

Participants received a single dose once weekly, which consisted of doses up to 9.0 mg petrelintide or placebo, administered subcutaneously.

All demographics were balanced across cohorts of healthy participants. The baseline characteristics of the subjects are shown in Table 3 below.

Table 3 – Participant parameters

		Total (n=16)
Sex	Male	12 (75%)
Race	Black or African American	0

	White	16 (100%)
Age (years)	Median	57
Weight (kg)	Median	86
BMI (kg/m ²)	Median	28.9

Body Composition (BOD POD®)

Body composition of the participants was assessed using the BOD POD® measurement system (COSMED, Rome, Italy), which used non-invasive air displacement plethysmography and whole body densitometry to estimate the amount of fat mass and fat free mass in the body. Whole body densitometry is based on the calculation of body density by measuring body mass and volume. Body mass was measured using an electronic scale, and body density was measured in a fiberglass test chamber. The endpoints body volume (L), body density (kg/L), fat mass (kg), % fat, fat free mass (kg), and % fat free mass (lean body mass), as all mass not measured as fat, were measured.

Plethysmography was performed on Day -1 (baseline), and Day 109.

Results

The change in percentage body fat, body volume, absolute lean body mass and percentage lean body mass are shown in Table 4 below.

Table 4 – Change from Day -1 to Day 109 after 1st Dosing (SAF)

Parameter [Unit]	Change from Baseline to Day 109 after 1 st Dosing	Statistics	Petrelintide (N=10)*	Placebo (N=4)
Body Fat Percent [%]	Change in %	Mean (SD)	-3.03 (2.452)	-2.25 (1.928)
Body Volume [L]	Change in L	Mean (SD)	-8.002 (3.8722)	-3.590 (5.0860)
Lean Body Mass [kg]	Change in kg	Mean (SD)	-2.61 (1.050)	0.12 (2.055)
Lean Body Mass Percent [%]	Change in %	Mean (SD)	3.03 (2.452)	2.25 (1.928)

* One participant dropped out after week 7; one participant dropped out after week 2

Mean proportion of Body Fat (measured in %) decreased by 3.03% in participates treated with petrelintide and decreased by 2.25% in participants dosed with placebo. Body volume decrease by 8.002 L in participates treated with petrelintide and decrease by 3.590 L in participants dosed with placebo. The lean Body mass (measured in kg) decrease by 2.61 kg in participates treated with petrelintide and increased by 0.12 kg in participants dosed with placebo. The mean proportion of lean body mass (measured in %) increased by 3.03% in participates treated with petrelintide and increased by 2.25% in in participants dosed with placebo.

All publications mentioned herein are herein incorporated by reference. Various modifications and variations of the described methods and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the

5 invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in biochemistry, molecular biology or related fields are intended to be within the scope of the following aspects.

ASPECTS OF THE INVENTION

The invention is described by way of the following numbered aspects:

1. A method of reducing body fat whilst preserving lean mass in a subject, the method
5 comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.
2. A method of inhibiting gain of body fat whilst preserving lean mass in a subject, the
method comprising administering to the subject petrelintide or a pharmaceutically acceptable
10 salt or solvate thereof.
3. The method of aspect 1 or aspect 2, wherein the method is a non-therapeutic
method.
- 15 4. A method of treating or preventing overweight, obesity, morbid obesity or a disease
associated with overweight, obesity or morbid obesity in a subject, wherein the method
reduces body fat whilst preserving lean mass in the subject, the method comprising
administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate
thereof.
20
5. Petrelintide or a pharmaceutically acceptable salt or solvate thereof for use in a
method of reducing body fat whilst preserving lean mass in a subject.
6. Petrelintide or a pharmaceutically acceptable salt or solvate thereof for use in a
25 method of treating or preventing overweight, obesity, morbid obesity or a disease associated
with overweight, obesity or morbid obesity in a subject, wherein the method reduces body fat
whilst preserving lean mass in the subject.
7. Use of petrelintide or a pharmaceutically acceptable salt or solvate thereof in
30 preparation of a medicament for reducing body fat whilst preserving lean mass in a subject.
8. Use of petrelintide or a pharmaceutically acceptable salt or solvate thereof in
preparation of a medicament for a method of treating or preventing overweight, obesity,
morbid obesity or a disease associated with overweight, obesity or morbid obesity in a
35 subject, wherein the method reduces body fat whilst preserving lean mass in the subject.

9. The method of aspect 4, petrelintide for use of aspect 6, or the use of aspect 8, wherein the method is a method of treating overweight in the subject.

10. The method of aspect 4 or aspect 9, petrelintide for use of aspect 6 or aspect 9, or
5 the use of aspect 8 or aspect 9, wherein the method is a method of treating obesity in the subject.

11. The method of any one of aspects 4, 9 and 10, petrelintide for use of any one of aspects 6, 9 and 10, or the use of any one of aspects 8, 9 and 10, wherein the method is a
10 method of treating morbid obesity.

12. The method of any one of aspects 4 and 9 to 11, petrelintide for use of any one of aspects 6 and 9 to 11, or the use of any one of aspects 8 and 9 to 11, wherein the method is a method of treating a disease associated with overweight, obesity and/or morbid obesity in
15 the subject.

13. The method of any one of aspects 4 and 9 to 12, petrelintide for use of any one of aspects 6 and 9 to 12, or the use of any one of aspects 8 and 9 to 12, wherein the method is a method of treating a disease associated with obesity and/or morbid obesity in the subject.
20

14. The method of any one of aspects 4 and 9 to 13, petrelintide for use of any one of aspects 6 and 9 to 13, or the use of any one of aspects 8 and 9 to 13, wherein the method is a method of preventing overweight in the subject.

25 15. The method of any one of aspects 4 and 9 to 14, petrelintide for use of any one of aspects 6 and 9 to 14, or the use of any one of aspects 8 and 9 to 14, wherein the method is a method of preventing obesity in the subject.

16. The method of any one of aspects 4 and 9 to 15, petrelintide for use of any one of aspects 6 and 9 to 15, or the use of any one of aspects 8 and 9 to 15, wherein the method is
30 a method of preventing morbid obesity in the subject.

17. The method of any one of aspects 4 and 9 to 16, petrelintide for use of any one of aspects 7 and 9 to 16, or the use of any one of aspects 8 and 9 to 16, wherein the method is
35 a method of preventing a disease associated with overweight, obesity and/or morbid obesity in the subject.

18. The method of any one of aspects 4 and 9 to 17, petrelintide for use of any one of aspects 6 and 9 to 17, or the use of any one of aspects 8 and 9 to 17, wherein the method is a method of preventing a disease associated with obesity and/or morbid obesity in the subject.

5

19. The method of aspect 4, petrelintide for use of aspect 6, or the use of aspect 8, wherein the method is a method of treating or preventing overweight, obesity or morbid obesity or preventing a disease associated with overweight, obesity, morbid obesity in the subject.

10

20. The method, petrelintide for use, or the use of any one of aspects 1 to 19, wherein the method is a method of inhibiting weight gain and/or reducing body weight in the subject.

21. The method, petrelintide for use, or the use of any one of aspects 1 to 20, wherein the method is a method of reducing food intake.

15

22. The method, petrelintide for use, or the use of any one of aspects 1 to 21, wherein the method is a method of reducing appetite.

20 23. The method, petrelintide for use, or the use of any one of aspects 1 to 22, wherein the method is a method of increasing satiety.

24. The method, petrelintide for use, or the use of any one of aspects 1 to 8, wherein the body fat of the subject is reduced by at least about 1%, such as by at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, or at least about 50%.

25

25. The method, petrelintide for use, or the use of any one of aspects 1 to 24, wherein the body fat of the subject is reduced over a period of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 30 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 1 month, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more than 10 years.

35

26. The method, petrelintide for use, or the use of any one of aspects 1 to 25, wherein the body fat of the subject is reduced over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.
27. The method, petrelintide for use, or the use of any one of aspects 1 to 26, wherein the method is a method of reducing body fat whilst preserving muscle in the subject.
28. The method, petrelintide for use, or the use of any one of aspects 1 to 27, wherein the method is a method of inhibiting gain of body fat whilst preserving muscle in the subject.
29. The method, petrelintide for use, or the use of any one of aspects 1 to 28, wherein the method increases the ratio of lean mass to body fat in the subject.
30. The method, petrelintide for use, or the use of any one of aspects 1 to 29, wherein the method increases the ratio of muscle to body fat in the subject.
31. The method, petrelintide for use, or the use of any one of aspects 1 to 30, wherein the lean mass of the subject is reduced insignificantly, or does not change, or increases.
32. The method, petrelintide for use, or the use of any one of aspects 1 to 31, wherein the lean mass of the subject is reduced insignificantly, or does not change, or increases over a period of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 30 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 1 month, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more than 10 years.
33. The method, petrelintide for use, or the use of any one of aspects 1 to 32, wherein the lean mass of the subject is reduced insignificantly, or does not change, or increases over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.

34. The method, petrelintide for use, or the use of any one of aspects 1 to 33, wherein the lean mass of the subject is reduced by less than about 1%, such as by about 0%.

5 35. The method, petrelintide for use, or the use of any one of aspects 1 to 34, wherein the lean mass of the subject is reduced by less than about 1% over a period selected from at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4
10 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more than 10 years.

36. The method, petrelintide for use, or the use of any one of aspects 1 to 35, wherein the lean mass of the subject is reduced by less than about 1% over a period selected from
15 about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.

20 37. The method, petrelintide for use, or the use of any one of aspects 1 to 36, wherein the lean mass of the subject increases by at least about 0.1%, such as by at least about 0.2%, at least about 0.3%, at least about 0.4%, at least about 0.5%, at least about 0.6%, at least about 0.7%, at least about 0.8%, at least about 0.9%, at least about 1.0%, at least about 1.1%, at least about 1.2%, at least about 1.3%, at least about 1.4%, at least about
25 1.5%, at least about 1.6%, at least about 1.7%, at least about 1.8%, at least about 1.9%, at least about 2.0%, at least about 2.5%, at least about 3%, at least about 4%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least
30 about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100%.

38. The method, petrelintide for use, or the use of any one of aspects 1 to 37, wherein the lean mass of the subject increases over a period selected from at least about 1 week, at
35 least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5

years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more than 10 years.

39. The method, petrelintide for use, or the use of any one of aspects 1 to 38, wherein
5 the lean mass of the subject increases over a period selected from about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 30 days, about 1 month, about 2 months, about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.

10 40. The method, petrelintide for use, or the use of any one of aspects 1 to 3, 5, 7 and 9 to 39, wherein the subject is of a healthy weight.

41. The method, petrelintide for use, or the use of aspect 40, wherein the subject has a Body Mass Index (BMI) of 18.5 to 24.9 corresponding to healthy weight.

15

42. The method, petrelintide for use, or the use of any one of aspects 1 to 39, wherein the subject is overweight.

43. The method, petrelintide for use, or the use of aspect 42, wherein the subject has a
20 BMI of 25.0 to 29.9 corresponding to overweight.

44. The method, petrelintide for use, or the use of any one of aspects 1 to 39, wherein the subject is obese.

25 45. The method, petrelintide for use, or the use of aspect 44, wherein the subject has a BMI of 30.0 to 39.9 corresponding to obese.

46. The method, petrelintide for use, or the use of any one of aspects 1 to 39, wherein the subject is morbidly obese.

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47. The method, petrelintide for use, or the use of aspect 46, wherein the subject has a BMI of 40.0 or higher corresponding to morbidly obese.

48. The method, petrelintide for use, or the use of any one of aspects 1 to 47, wherein
35 the subject has diabetes.

49. The method, petrelintide for use, or the use of any one of aspects 1 to 48, wherein the subject suffers from a disease associated with overweight, obesity or morbid obesity.

50. The method, petrelintide for use, or the use of aspect 49, wherein the disease
 5 associated with overweight, obesity or morbid obesity is selected from the group consisting of hypertension, dyslipidemia, sleep apnea, cardiovascular disease, binge-eating disorder, Prader-Willi syndrome, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease, respiratory problems, degeneration of cartilage, osteoarthritis, reproductive health complications such as infertility, Alzheimer's disease, diabetes, type 1
 10 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, atherogenic dyslipidemia, hepatic steatosis ("fatty liver"), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatotic liver disease (MASLD),
 15 metabolic (dysfunction) associated fatty liver disease (MAFLD), metabolic dysfunction-associated steatohepatitis (MASH), kidney failure, arteriosclerosis, atherosclerosis, macrovascular disease, microvascular disease, diabetic heart disease, diabetic cardiomyopathy, heart failure as a diabetic complication, coronary heart disease, peripheral artery disease or stroke, and combinations thereof.

20 51. The method, petrelintide for use, or the use of any one of aspects 1 to 50, wherein the subject suffers from a disease associated with gain of body fat.

52. The method, petrelintide for use, or the use of any one of aspects 1 to 51, wherein
 25 the subject suffers from a disease associated with loss of lean mass.

53. The method, petrelintide for use, or the use of any one of aspects 1 to 52, wherein the subject suffers from a disease associated with gain of body fat and loss of lean mass.

30 54. The method, petrelintide for use, or the use of any one of aspects 1 to 53, wherein the subject suffers from a disease selected from sarcopenic obesity, Duchenne muscular dystrophy (DMD), Charcot-Marie-Tooth disease (CMT), chronic obstructive pulmonary disease (COPD), McArdle disease, hypothyroidism, testosterone deficiency syndrome (TD), heart failure and anaemia.

35 55. The method, petrelintide for use, or the use of any one of aspects 1 to 54, wherein the subject is following a dietary regimen.

56. The method, petrelintide for use, or the use of any one of aspects 1 to 55, wherein petrelintide is formulated as a pharmaceutical composition.
- 5 57. The method, petrelintide for use, or the use of aspect 56, wherein the composition comprises a pharmaceutically acceptable carrier, excipient or vehicle.
58. The method, petrelintide for use, or the use of aspect 56 or aspect 57, wherein the pharmaceutical composition is a stable aqueous liquid pharmaceutical composition.
- 10 59. The method, petrelintide for use, or the use of any one of aspects 56 to 58, wherein petrelintide is present in the composition at a concentration of from about 0.4 mg/ml to about 25 mg/ml.
- 15 60. The method, petrelintide for use, or the use of any one of aspects 56 to 59, wherein petrelintide is present in the composition at a concentration of
(a) at least about 0.4 mg/ml, at least about 0.5 mg/ml, at least about 0.6 mg/ml, at least about 1.2 mg/ml, or at least about 2.5 mg/ml; and/or
(b) up to about 25 mg/ml, up to about 20 mg/ml, up to about 15 mg/ml, or up to about 10
20 mg/ml; and/or
(c) about 3 mg/ml to about 12 mg/ml, e.g. about 3 mg/ml to about 7 mg/ml or about 8 mg/ml to about 12 mg/ml, e.g. about 5 mg/ml or about 10 mg/ml.
- 25 61. The method, petrelintide for use, or the use of any one of aspects 56 to 60, wherein the composition comprises a buffer at a concentration of about 0.5 mM to about 25 mM.
62. The method, petrelintide for use, or the use of aspect 61, wherein the buffer is present at a concentration of about 0.5 mM to about 20 mM, about 0.5 mM to about 15 mM, about 1 mM to about 15 mM, about 1 mM to about 12 mM, about 3 mM to about 7 mM,
30 about 8 mM to about 12 mM, or about 5 mM or about 10 mM.
63. The method, petrelintide for use, or the use of aspect 61 or aspect 62, wherein the buffer is phosphate, histidine or citrate.
- 35 64. The method, petrelintide for use, or the use of aspect 61, wherein the buffer is TRIS buffer, and wherein the buffer is present at about 15 mM to about 25 mM, e.g. about 17 mM to about 23 mM, e.g. about 20 mM.

65. The method, petrelintide for use, or the use of any one of aspects 56 to 64, wherein the composition has a pH of about 5.8 to about 6.9.

5 66. The method, petrelintide for use, or the use of aspect 65, wherein the pH is about 6.2 to about 6.8, about 6.4 to about 6.6, or about 6.5.

67. The method, petrelintide for use, or the use of any one of aspects 56 to 66, wherein the composition comprises a tonicity modifier.

10

68. The method, petrelintide for use, or the use of any one of aspects 56 to 67, wherein the composition comprises a preservative.

69. The method, petrelintide for use, or the use of aspect 68, wherein the preservative is
15 meta-cresol, phenol, methylparaben, ethylparaben, propylparaben, butylparaben, chlorobutanol, benzyl alcohol, phenylmercuric nitrate, thimerosal, sorbic acid, potassium sorbate, benzoic acid, chlorocresol or benzalkonium chloride.

70. The method, petrelintide for use, or the use of any one of aspects 1 to 69, wherein
20 petrelintide is provided as a chloride salt.

71. The method, petrelintide for use, or the use of any one of aspects 1 to 70, wherein petrelintide is administered to the subject at a dose of about 0.0001 to about 100 mg/kg body weight per day, such as about 0.0005 to about 50 mg/kg body weight per day, such as about
25 0.001 to about 10 mg/kg body weight per day, such as about 0.01 to about 1 mg/kg body weight per day.

72. The method, petrelintide for use, or the use of any one of aspects 1 to 71, wherein petrelintide is administered to the subject at a dose of about 2 nmol/kg body weight or about
30 10 nmol/kg body weight.

73. The method, petrelintide for use, or the use of any one of aspects 1 to 72, wherein petrelintide is administered to the subject once daily, twice daily, once every two, three, four, five or six days, once weekly, twice weekly, once monthly or twice monthly.

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74. The method, petrelintide for use, or the use of aspect 73, wherein petrelintide is administered to the subject twice daily, once every two days or once every four days.

75. The method, petrelintide for use, or the use of any one of aspects 1 to 74, wherein petrelintide is administered to the subject by injection, such as by subcutaneous (sc), intramuscular (im) or intravenous (iv) injection.

CLAIMS

1. A method of reducing body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.
- 5 2. A method of inhibiting gain of body fat whilst preserving lean mass in a subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.
- 10 3. A method of treating or preventing overweight, obesity, morbid obesity or a disease associated with overweight, obesity and/or morbid obesity in a subject, wherein the method reduces body fat whilst preserving lean mass in the subject, the method comprising administering to the subject petrelintide or a pharmaceutically acceptable salt or solvate thereof.
- 15 4. The method of any one of claims 1 to 3, wherein the body fat of the subject is reduced by at least about 1%, such as by at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, or at least about 50%.
- 20 5. The method of any one of claims 1 to 4, wherein the body fat of the subject is reduced over a period selected from at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 30 days, at least about 1 month, at least about 2 months, at least about 6 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more than 10 years.
- 25 6. The method of any one of claims 1 to 5, wherein the method is a method of reducing body fat whilst preserving muscle in the subject
- 30 7. The method of any one of claims 1 to 6, wherein the method is a method of inhibiting gain of body fat whilst preserving muscle in the subject.
- 35 8. The method of any one of claims 1 to 7, wherein the lean mass of the subject is reduced insignificantly, or does not change, or increases.

9. The method of any one of claims 1 to 8, wherein the subject is overweight, obese or morbidly obese.

5 10. The method of any one of claims 1 to 9, wherein the subject suffers from a disease associated with overweight, obesity or morbid obesity.

11. The method of claim 10, wherein the disease associated with overweight, obesity or morbid obesity is selected from the group consisting of hypertension, dyslipidemia, sleep
10 apnea, cardiovascular disease, binge-eating disorder, Prader-Willi syndrome, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease, respiratory problems, degeneration of cartilage, osteoarthritis, reproductive health complications such as infertility, Alzheimer's disease, diabetes, type 1 diabetes, type 2 diabetes, pre-diabetes, insulin resistance syndrome, impaired glucose tolerance (IGT), disease states associated
15 with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, atherogenic dyslipidemia, hepatic steatosis ("fatty liver"), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic (dysfunction) associated fatty liver disease (MAFLD), metabolic dysfunction-associated steatohepatitis (MASH), kidney failure,
20 arteriosclerosis, atherosclerosis, macrovascular disease, microvascular disease, diabetic heart disease, diabetic cardiomyopathy, heart failure as a diabetic complication, coronary heart disease, peripheral artery disease or stroke, and combinations thereof.

12. The method of any one of claims 1 to 11, wherein the subject suffers from a disease
25 associated with gain of body fat and loss of lean mass.

13. The method of any one of claims 1 to 12, wherein the subject suffers from a disease selected from sarcopenic obesity, Duchenne muscular dystrophy (DMD), Charcot-Marie-Tooth disease (CMT), chronic obstructive pulmonary disease (COPD), McArdle disease,
30 hypothyroidism, testosterone deficiency syndrome (TD), heart failure and anaemia.

14. The method of any one of claims 1 to 13, wherein petrelintide is formulated as a pharmaceutical composition, preferably wherein the pharmaceutical composition is a stable aqueous liquid pharmaceutical composition.

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15. The method of any one of claims 1 to 14, wherein the subject is following a dietary regimen.

16. The method of any one of claims 1, 2 and 4 to 15, wherein the method is a non-therapeutic method.
- 5 17. The method of claim 16, wherein the subject is of a healthy weight or is overweight.