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(54) **Title:** USE OF A GROWTH HORMONE SECRETATOGUE FOR INCREASING OR MAINTAINING LEAN BODY MASS AND/OR FOR TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

(57) **Abstract:** The present invention relates to a method for increasing or maintaining lean body mass in an individual in need thereof, by administering a secretagogue. The present invention also relates in another aspect to the use of a secretagogue for the production of a medicament for use in increasing or maintaining an individual's lean body mass, preferably in an individual suffering from, or at risk of suffering from, cachexia, such as cancer cachexia.

Use of a growth hormone secretagogue for increasing or maintaining lean body mass and/or for treatment of chronic obstructive pulmonary disease

This application claims priority from Danish patent application numbers PA 2005 00242, filed 16th February 2005, and PA 2004 01657, filed 27th October 2004, which are hereby incorporated by reference in their entirety. This application is a nonprovisional of U.S. provisional application Serial No. 60/653,116 filed 16th February 2005, which is hereby incorporated by reference in its entirety. All patent and non-patent references cited in the present application, are also hereby incorporated by reference in their entirety.

Field of invention

The present invention relates in one aspect to a method for increasing or maintaining lean body mass in an individual in need thereof. In another aspect, the present invention relates to a method for treatment of an individual suffering from, or at risk of suffering from, chronic obstructive pulmonary disease (COPD).

Background of invention

Ghrelin is a bioactive peptide which originally was described to be involved in the control of GH secretion but later found to be a major regulator of appetite, food intake and energy homeostasis (Kojima M et al., Trends Endocrinol Metab 12:118-122; Nakazato M et al., 2001, Nature 409:194-198). Similar to many other bioactive peptides, ghrelin probably acts both as a hormone, a paracrine substance and as a neurotransmitter. The story of ghrelin, its receptor and synthetic compounds acting through this receptor unraveled in a unique "reverse" order. In the eighties a synthetic hexa-peptide from a series of opioid-like peptides was found to be able to release growth hormone (GH) from isolated pituitary cells (Bowers CY et al., 1980, Endocrinology 106:663-667). Since this action was independent of the growth hormone releasing hormone (GHRH) receptor, several pharmaceutical companies embarked upon drug discovery projects based on this hexa-peptide GH secretagogue (GHS) and its putative receptor. Several series of potent and efficient peptide as well as non-peptide GH secretagogues were consequently described in the mid nineties (Bowers CY et al., Endocrinology 114:1537-1545; Patchett AA et al., 1995; Proc Natl Acad Sci U S A 92:7001-7005; Smith RG et al., Science 260:1640-1643). However, it was only several years later that the receptor through

which these artificial GH secretagogues acted was eventually cloned and shown to be a member of the 7TM G protein coupled receptor family (Howard AD et al., Science 273:974-977; Smith RG et al., 1997 Endocr Rev 18:621-645). In 1999, the endogenous ligand for this receptor, the hormone ghrelin, was finally discovered (Kojima M et al., 1999, Nature 402:656-660). The main site for ghrelin production is the stomach, where the peptide is found in classical endocrine cells in the gastric mucosa.

From here, ghrelin is secreted in the pre-meal situation which results in a sharp, short-lived surge in plasma levels of ghrelin before the meal and starting 1-2 hours before and lasting a short while after initiation of the meal. Since ghrelin is the only peripherally produced orexigenic (appetite promoting) substance it is believed that the increase in plasma levels of ghrelin is crucial for the initiation of the meal.

In its role as a key initiator of appetite, ghrelin released from the endocrine cells in the mucosa of the GI tract may act both locally as a paracrine substance and centrally as a hormone.

Previously, ghrelin has been administered by continuous infusions for 270 minutes, which has shown that an increase in food intake can be obtained through intravenous administration of ghrelin (Wren et al JCEM 2001; 86(12)5992-5995).

Chronic obstructive pulmonary disorder (COPD) and weight loss

Weight loss is common among patients with chronic obstructive pulmonary disease (COPD), occurring in approximately 35-60% of patients with moderate to severe disease. Low body weight and weight loss are independent predictors of morbidity and mortality in COPD (Berry JK et al., Reversal of chronic obstructive pulmonary disease-associated weight loss. Are there pharmacological treatment options ?. *Drugs* 2004;**64**:1041-1052).

In patients referred to lung transplantation a lean body mass < 60% of normal is associated with an increased waiting list mortality (31% vs. 12%, *p=0.03*) (Schwebel C et al., Prevalence and consequence of nutritional depletion in lung transplant candidates. *Eur Respir J* 2000;**16**:1050-55).

Similarly in patients undergoing lung transplantation the 3-months mortality is higher among patients with a body mass index (BMI) below 17 kg/m^2 (odds ratio of dying 3.7, *p=0.09*) (Madill J et al.; Toronto Lung Transplant Program. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. *J Heart Lung Transplant* 2001;**20**:288-96.)

Weight gain in the first year after transplantation has been shown to reduce the risk of subsequent mortality (hazard ratio 0.61(95% CI 0.41-0.90, *p<0.05*) (Singer LG et al., International Lung Transplant Database Study Group. Weight gain after lung transplantation. *J Heart Lung Transplant* 2003;**22**:894-902.).

Summary of the Invention

The present invention relates in one aspect to a method for increasing or maintaining lean body mass in an individual in need thereof, by administering a ghrelin receptor 1a secretagogue ("GHS-R1a secretagogue"), such as a ghrelin-like compound.

The present invention also relates to the use of a GHS-R1a secretagogue, such as a ghrelin-like compound that stimulates the ghrelin receptor 1a (GHS-R1a), for the production of a medicament for use in increasing or maintaining an individual's lean body mass, preferably in an individual suffering from, or at risk of suffering from, cachexia, such as cancer cachexia.

Thus, the present invention relates to the use of a GHS-R1A secretagogue, such as a ghrelin-like compound, for the preparation of a medicament for use in increasing or maintaining an individual's lean body mass, preferably for increasing or maintaining an individual's percentage lean body mass. Additionally, said increase or maintenance of lean body mass may occur in combination with:

a) prophylaxis or treatment of cachexia, and/or

b) stimulation of appetite, and/or

c) stimulation of food intake, and/or

d) stimulation of weight gain, and/or

e) increasing body fat mass, and/or

f) improvement in anticancer therapy tolerability and/or

g) improvement in anticancer therapy response rate,

including any combination of the above,

in an individual by administering a dosage of said medicament to the individual.

Thus, in addition to administering a GHS-R1a secretagogue to primarily increase or maintain an individual's lean body mass, the secretagogue may be administered in an amount sufficient to cause any of the above secondary effects, such as by administering a dosage comprising an amount of the GHS-R1a secretagogue or a salt thereof equivalent to from 0.3 μg to 600 mg ghrelin.

Preferred combinations of the above secondary effects are: a); b); c); d); and e) in isolation; as well as a)+b; a) + c); a) + d); a) + e); b) + c); b) + d); b) + e); a) + c) + d); a) + c) + e); a) + d) + e); a) + c) + d) + e); b) + c) + d); b) + c) + e); b) + d) + e); b) + c) + d) + e); a) + b) + c) + f) + g); f) + g); c) + f) + g) + a); a)+ f) + g).

In one embodiment, said increase or maintenance of lean body mass may occur in combination with:
a) prophylaxis or treatment of cachexia, and/or
b) stimulation of appetite,

in an individual by administering an effective dosage of a medicament comprising a GHS-R1a secretagogue to said individual, preferably prior to a meal,

wherein the secretagogue is preferably a ghrelin-like compound, more preferably a ghrelin-like compound which comprises a structure defined by formula I, described herein.

Thus, in one embodiment, said increase or maintenance of lean body mass may occur in combination with the treatment or prophylaxis of cancer cachexia, in particular, caused by the sub-types of cancer that induce a high degree of cachexia with an increase of REE, such as Lung cancer and Pancreatic cancer. In a preferred embodiment the invention relates to the use of a GHS-R1a secretagogue, such as a ghrelin-like compound, such as a ghrelin-like compound comprising a structure

defined by formula I, described above, for the preparation of a medicament for the increase or maintenance of lean body mass, in combination with treatment or prophylaxis of cancer cachexia.

In a second aspect, the present invention relates to the use of a GHS-R1a secretagogue, such as a ghrelin-like compound, for the preparation of a medicament for the treatment of an individual suffering from, or at risk of suffering from, chronic obstructive pulmonary disease (COPD). The present invention further relates to a method for treatment of an individual suffering from, or at risk of suffering from, chronic obstructive pulmonary disease, by administering a GHS-R1a secretagogue, such as a ghrelin-like compound.

Thus, in a second aspect, the invention relates to the use of a a GHS-R1a secretagogue compound for the preparation of a medicament for the stimulation of appetite, food intake and/or weight gain in an individual suffering from, or at risk of suffering from, COPD.

Furthermore, the invention relates to a method for stimulating appetite, food intake and/or weight gain in an individual suffering from, or at risk of suffering from, COPD, said method comprising administration of a GHS-R1a secretagogue to said patient.

Accordingly, the invention relates to the use of a GHS-R1a secretagogue compound for the preparation of a medicament for

a) stimulation of appetite, and/or
b) stimulation of food intake, and/or
c) stimulation of weight gain, and/or
d) increasing body fat mass, and/or
e) increasing lean body mass,

including any combination of the above,

by administering a dosage of said medicament in an individual suffering from, or at risk of suffering from, COPD. Optionally, said individual is a lung transplant patient that will undergo, is undergoing or has undergone a lung transplant.

Preferred combinations are: a); b); c); d); and e); in isolation; as well as a)+b); a) + c); a) + d); a) + e); b) + c); b) + d); b) + e); d) +e); c)+ d)+ e) ; a) + c) + d); a) + c) + e); ; a) + d) + e); a) + c) + d) + e); b) + c) + d); b) + c) + e); b) + d) + e); and b) + c) + d) + e).

Preferably, said GHS-R1a secretagogue is a ghrelin-like compound, such as a ghrelin-like compound comprising a structure defined herein below.

The orexigenic and metabolic effects of GHS-R1a secretagogues, such as ghrelin, reduce the morbidity and mortality in patients undergoing lung transplantation. Furthermore, these effects improve their quality of life.

Patients particularly in need of treatment are ones having a lean body mass of less than 80% of normal, such as less than 60% of normal and/or a body mass index below 17 kg/m^2.

In the case of lung transplant patients, the medicament may be given during the pre-operative period, the peri-operative period and/or post-operative period. In order to optimise the recipient's nutritional status prior to, during and after organ transplantation, secretagogue therapy is preferably initiated at the time of referral to transplantation and continued throughout the peri- and postoperative period until body weight has been normalised. Thus, in a preferred embodiment, the medicament is given during the pre-operative, the peri-operative and the post-operative period.

In preferred embodiments of the present invention, the medicament is preferably given until the lean body mass is more than 60% of normal, preferably more than 80% of normal, more preferably more than more 90% of normal.

In all aspects of the present invention, it is preferred that the GHS-R1a secretagogue is a ghrelin-like compound which comprises a structure defined by formula I

$Z^1 - (X^1)_m - (X^2) - (X^3)_n - Z^2$, wherein

Z^1 is an optionally present protecting group

each X^1 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

X^2 is any amino acid selected from naturally occurring and synthetic occurring amino acids, said amino acid being modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

each X^3 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

wherein one or more of X^1 and X^3 optionally may be modified by a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

Z^2 is an optionally present protecting group,

m is an integer in the range of from 1-10

n is 0 or an integer in the range of from 1-35.

In one embodiment of the invention the GHS-R1a secretagogue is administered with a substance capable of increasing the half-life of the GHS-R1a secretagogue, for example by incorporating the secretagogue compound into liposomes, micelles, iscoms, and/or microspheres or other transport molecules. This is of particular interest when an amino acid residue of the GHS-R1a secretagogue is modified with a bulky hydrophobic group and it is desirable to protect the modified amino acid from degradation. Accordingly, the invention further relates to a pharmaceutical composition comprising a GHS-R1a secretagogue or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carriers, vehicles and/or excipients, said composition further comprising transport molecules, such as liposomes, micelles, and/or microspheres.

In all embodiments of the present invention, the medicament can be administered as a bolus injection or by fast running infusion, i.e. an infusion preferably lasting less than 120 minutes, such as less than 90 minutes, for example less than 60 minutes, such as less than 45 minutes, such as less than 30 minutes, for example less than 25 minutes, such as less than 20 minutes, such as less than 15 minutes, for example less than 12 minutes, such as less than 10 minutes, such as less than 8 minutes, for example less than 6 minutes, such as less than 5 minutes, such as less than 4 minutes, for example less than 3 minutes, such as less than 2 minutes, such as less than 1 minute.

A Y-formed catheter can be used for rapid infusion. A solution of the GHS-R1a secretagogue can be injected through one catheter entry port and optionally saline can, if desirable, be injected through the other catheter entry port.

The bolus injection or the fast running infusion can be administered prior to a meal or during a meal as described in more detail herein below. In one preferred embodiment the medicament is administered as a bolus. The bolus is preferably administered subcutaneously.

Detailed Description of the Invention

Definitions

Affinity: the strength of binding between receptors and their ligands, for example between the GHR1a receptor and a secretagogue, such as a ghrelin-like compound.

Amino Acid Residue: An amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are preferably in the "L" isomeric form. However, the amino acid encompasses every amino acid such as L-amino acid, D-amino acid, alpha -amino acid, beta -amino acid, gamma -amino acid, natural amino acid and synthetic amino acid or the like as long as the desired functional property is retained by the polypeptide. NH_2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxy terminus of a polypeptide. In

keeping with standard polypeptide, abbreviations for amino acid residues are shown in the following Table of Correspondence:

TABLE OF CORRESPONDENCE

SYMBOL		
1-Letter	3-Letter	AMINO ACID
Y	Tyr	tyrosine
G	Gly	glycine
F	Phe	phenylalanine
M	Met	methionine
A	Ala	alanine
S	Ser	serine
I	Ile	isoleucine
L	Leu	leucine
T	Thr	threonine
V	Val	valine
P	Pro	proline
K	Lys	lysine
H	His	histidine
Q	Gln	glutamine
E	Glu	glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	tryptophan
R	Arg	arginine
D	Asp	aspartic acid
N	Asn	asparagine
B	Asx	Asn and/or Asp
C	Cys	cysteine
X	Xaa	Unknown or other

It should be noted that all amino acid residue sequences represented herein by formulae have a left-to-right orientation in the conventional direction of amino terminus to carboxy terminus. In addition, the phrase "amino acid residue" is broadly defined to include the amino acids listed in the Table of Correspondence and modified and non-naturally occurring amino acids. Furthermore, it should be noted

that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues or a covalent bond to an amino-terminal group such as NH_2 or acetyl or to a carboxy-terminal group such as COOH.

Anti-neoplastic treatment: Treatment aimed at halting or reducing abnormal tissue growth (such as a neoplasm) in an individual. Examples of such treatment include cancer therapies, such as radiotherapy or chemotherapy.

Appetite: Appetite in an individual is assessed by measuring the amount of food ingested and by assessing the individual's desire to eat. Appetite (for example hunger) is typically assessed with a short questionnaire given to individuals on a random basis several times a week. Typically, subjects rate their hunger, preoccupation with food, and desire to eat greater quantities and different types of food by answering the questions using analogue scales ranging from 1, not at all, to 5, extremely.

BMI measures your height/weight ratio. It is determined by calculating weight in kilograms divided by the square of height in meters. The BMI "normal" range is 19-22.

Body fat mass: Body fat mass can be measured e.g. by the skin fold technique: In this technique, a pincer-type caliper is used to measure subcutaneous fat by determining skin fold thickness at representative sites on the body. These skin fold measurements are then used to compute body fat by either adding the scores from the various measurements and using this value as an indication of the relative degree of fatness among individuals or by using the measurements in mathematical equations that have been developed to predict percent body fat. Another method for measuring body fat mass is using a DEXA scan or MRI.

Concentration equivalent: A concentration equivalent is an Equivalents dosage being defined as the dosage of a ghrelin-like compound having in vitro and/or in vivo the same response as evaluated from a dosage-response curve of wild-type ghrelin.

Dissociation constant, Kd: a measure to describe the strength of binding (or affinity

or avidity) between receptors and their ligands, for example the GHR1a receptor and a ghrelin-like compound. The smaller Kd the stronger binding.

Fusion Polypeptide: A polypeptide comprised of at least two polypeptides and a linking sequence to operatively link the two polypeptides into one continuous polypeptide. The two polypeptides linked in a fusion polypeptide are typically derived from two independent sources, and therefore a fusion polypeptide comprises two linked polypeptides not normally found linked in nature.

Ghrelin: a polypeptide as described in Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K 1999, "Ghrelin is a growth-hormone-releasing acylated petide from stomach". Nature 402:656-660. Human 28 aa ghrelin has the amino acid of SEQ ID NO: 1.

Ghrelin-like compound: the term "ghrelin-like compound" as used herein refers to any compound which mimics the function of wild-type ghrelin, such as any of the compounds described herein, such as further described in the section below entitled "Functionality", particularly leading to the desired therapeutic effects described herein, such as increase or maintenance of lean body mass and optionally stimulation of appetite and/or treatment and/or prophylaxis of cachexia. The ghrelin-like compound may be defined by the formula I:

$Z^1 - (X^1)_m - (X^2) - (X^3)_n - Z^2$, wherein

Z^1 is an optionally present protecting group

each X^1 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

X^2 is any amino acid selected from naturally occurring and synthetic occurring amino acids, said amino acid being modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

each X^3 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

wherein one or more of X^1 and X^3 optionally may be modified by a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

Z^2 is an optionally present protecting group,

m is an integer in the range of from 1-10

n is 0 or an integer in the range of from 1-35.

Furthermore, a ghrelin-like compound has a functionality leading to the desired therapeutic effects described herein. A preferred ghrelin-like compound is wild-type ghrelin (SEQ ID NO:1).

GHS: growth hormone secretagogue

GHS-R 1a: the receptor for GHS. GHS-R 1a is also denoted GHS 1a, or as the ghrelin receptor 1a.

Individual: A living animal or human susceptible to a pathogical condition. In preferred embodiments, the subject is a mammal, including humans and non-human mammals such as dogs, cats, pigs, cows, sheep, goats, horses, rats, and mice. In the most preferred embodiment, the subject is a human.

Isolated: is used to describe the various secretagogue compounds, ghrelin-like compounds, polypeptides and nucleotides disclosed herein, that have been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified.

Lean body mass and "increased or maintained lean body mass":

Lean body mass is defined herein as body weight minus body fat; primarily muscle, bone and other non-fat tissue. A number of methods may be used for calculating an individual's percentage lean body mass:

1) Body mass index (BMI) calculated as body weight (kg) divided by the square of height (m) is used to describe the severity of obesity. BMI correlates reasonably well with fat mass and using age- and sex- specific prediction equations, the relative fat mass can be predicted with an error of ~5% in most subjects (Gallagher,D., et al., 1996 Am J Epidemiol 143:228-239).

2) Waist-to-hip ratio (WHR): in the mid-eighties WHR was shown to be particularly well correlated to increased visceral adipose tissue as measured by computed tomography (CT) or magnetic resonance (MRI) waist scans ($r=0.88$, $P<0.001$) (Seidell,J.C., et al., 1989, INT.J.OBES. 13:289-303; Ashwell,M., et al., 1985,. Br Med J (Clin Res Ed) 290:1692-1694). Furthermore, WHR has been tightly correlated to total body fat as assessed by CT ($r=0.97$, $p<0.0001$) (Despres,J.P., et al., 1991 American journal of clinical nutrition 54:471-477). It has since been used as a valuable surrogate measure of visceral adipose tissue. WHR is a useful measure to quantify either inter-individual differences or individual changes over time (Gallagher,D., et al., 1996 Am J Epidemiol 143:228-239).

3) Computed Tomography (CT) provides unique direct information on body composition and permits quantification of all major tissue system level components (adipose tissue, skeletal muscle, visceral organs and bone) (Hemmingsson,A et al., 1982, Acta Radiol 23:149-151). CT moreover has the advantage of permitting the partition of the total adipose tissue (AT) mass into its subcutaneous and visceral components (Tokunaga,K., et al., INT.J.OBES. 7:437-445). This leaves CT with a significant advantage for body composition studies because of its potential for monitoring changes in the visceral AT and subcutaneous AT compartments separately, information, which is at present not available with any alternative in vivo technique except for MRI. CT scan for the assessment of body composition can be performed as either multi-slice covering the whole body and wherefrom calculations of whole body and regional AT can be derived. The CT method has been extensively validated. Animal and human cadaver studies have been used to verify the accuracy of the AT-estimate and its anatomical distribution showing a high correlation and therefore by some suggested as a "gold standard" against which to compare other non-invasive methods (Kvist, H., et al., 1988, INT.J.OBES. 12:249-266). At present, the most accurate in vivo methods of measuring body composition

are multi-slice MRI and CT (Rossner,S., 1990, INT.J.OBES. 14:893-902). The highest precision is obtained using multi-slice CT scans (CV<1%) (Jensen,M.D., et al., 1995, American journal of clinical nutrition 61:274-278). However, due to radiation exposure, multi-slice CT is unsuitable for studies requiring repeated measurements on the same subject. A regional scan assessing the AT at the abdominal level is highly correlated with total AT mass in both men and women (r=0.92 and 0.97, respectively) (Despres,J.P., et al., American journal of clinical nutrition 54:471-477; Koester,R.S., et al., 1992, Int J Obes Relat Metab Disord 16:543-554; Lemieux,S., et al., 1993, American journal of clinical nutrition 58:463-467).

4) Magnetic Resonance Imaging (MRI) has the same imaging properties as CT, but does not require the use of radiation and therefore may be preferred to CT.

5) Bioelectric Impedance Analysis (BIA): In BIA an alternating current at one or more frequencies is introduced via electrodes and the body impedance (=resistance) to the electrical flow is measured. Body water poses the least impedance to the electric current, whereas body fat and bone provides the most (Heymsfield,S.B., et al., 1997, *Annu Rev Nutr* 17:527-558). BIA is inexpensive, easy to use and portable, and is therefore frequently used in combination with anthropometric measurements to predict body composition. BIA was reviewed by an expert panel in 1996, evaluating the method to provide a reliable estimate under most conditions and to be useful in healthy individuals and diseases where no major disturbances of water distribution are prominent.

6) Dual energy X-ray Absorptiometry ("DXA" or "DEXA"): DXA is a direct, operator independent, non-invasive method to estimate body composition. Measurements are based on the differential attenuation of two X-rays as they pass through the body. It distinguishes bone mineral from soft tissue and subsequently divides the latter into FM and FFM (Pietrobelli,A., et al., 1996, *Am J Physiol* 271:E941-E951). The analyzed data yield information about composition of the whole body but also permits regional body composition determination. DXA has been widely validated and appear to be a precise (CV~1%(bone), CV~3%(LBM and FM) and simple way of measuring total and regional FM and LBM. Exposure to radiation is minimal (2-5 μSv) in most DXA machines.

In one embodiment of the invention described herein, it is preferred that the increase or maintenance of lean body mass is measured using DXA. In another preferred

embodiment, said increase or maintenance of lean body mass is measured using MRI.

"Increasing lean body mass" and variations on this phrase can mean e.g. either increasing total lean body mass in an individual and/or increasing an individual's overall percentage lean body mass (e.g. as compared to total body mass), such as increasing an individual's percentage lean body mass by more than 0.5 %, such as more than 0.75%, such as more than 1%, for example more than 1.25%, such as more than 1.5%, for example more than 1.75%, such as more than 2%, for example more than 2.25%, such as more than 2.5%, for example more than 2.75%, such as more than 3%, for example more than 3.25%, such as more than 3.5%, for example more than 3.75%, such as more than 4%, for example more than 4.25%, such as more than 4.5%, for example more than 4.75%, such as more than 5%, for example more than 5.25%. In one embodiment it is preferred that the increase lean body mass is caused by an increase in muscle mass, as measured using for instance MRI or CT. In another preferred embodiment, said increase of lean body mass may be with respect to a control group of individuals not treated with the GHS-R1a secretagogue. By "maintaining" lean body mass and grammatical variants thereof, is meant that said GHS-R1a secretagogue acts to counteract loss of an individual's lean body mass, by preventing or reducing a decrease in total amount of lean body mass (as measured using for instance DEXA scans). In all cases, by "increase or maintenance of lean body mass" herein is meant that the increase or maintenance of lean body mass is caused by the beneficial effects of the secretagogue itself on the individual thus treated, instead of being caused by e.g. increased exercise or other factors not directly related to a GHS-R1A secretagogue's metabolic effects.

Lung transplant patient: An individual who will undergo, is undergoing or has undergone a lung transplantation. Accordingly, the term includes patients that will undergo lung transplantation, but are e.g. preparing for the transplantation or on a waiting list.

Modified amino acid: an amino acid wherein an arbitrary group thereof is chemically modified. In particular, a modified amino acid chemically modified at the alpha -carbon atom in an alpha -amino acid is preferable.

Non-acylated GHS-R1a secretagogue: a GHS-R1a secretagogue, such as a ghrelin

like-compound as defined herein, which does not contain an acyl group attached to any of its constitutent amino acids.

Palliative treatment: a treatment which relieves or sooths the symptoms of a disease or disorder but without curing the underlying disease.

Polypeptide: The phrase polypeptide refers to a molecule comprising amino acid residues which do not contain linkages other than amide linkages between adjacent amino acid residues.

Receptor: A receptor is a molecule, such as a protein, glycoprotein and the like, that can specifically (non-randomly) bind to another molecule.

Secretagogue: a GHS-R1a secretagogue, e.g. a substance stimulating growth hormone release, such as ghrelin or a ghrelin-like compound. A secretagogue according to the invention may for example be selected from the group of:
L-692-429, L-692-585 (Benzoelactam compounds)
MK677 (Spiroindaner)
G-7203, G-7039, G-7502 (Isonipecotic acid peptidomimetic)
NN703, ipamorelin.

GHRP-1	(Bower)
GHRP-2	(Bower)
GHRP-6	(Bower)
Hexarelin	(Europeptide)
Ipamorelin	(Novo Nordisk)
NNC 26-0235	(Novo Nordisk)
G-7039	(Genentech)
G-7502	(Genentech)
NNC26-0323	(Genentech)
NN703	(Novo Nordisk)
NNC26-0722(NN)	(Novo Nordisk)
L-692,429	(Merck)
L-692,585	(Merck)
NNC26-0610(NN)	(Novo Nordisk)
MK-677	(Merck)

L-163,540	(Merck)
CP-424,391	(Pfizer)
EP51319	(Theratechnology)
RC-1291	(Rejuvenon)
BIM28125	(IPSEN)
BIM28131	(IPSEN)

In particular the secretagogue is a ghrelin-like compound, including 28 aa human ghrelin. The secretagogue may in one embodiment be non-acylated, for instance a non-acylated form of ghrelin or a non-acylated ghrelin-like compound. In one embodiment, another bulky group (such as e.g. a cholesterol or tryptophan moiety) replaces the usual acyl group on said non-acylated ghrelin-like compound.

Surfactant molecule: Molecule comprising a hydrophobic part and a hydrophilic part, i.e. molecule capable of being present in the interphase between a lipophilic phase and a hydrophilic phase.

Indications

In one aspect, the present invention relates to the use of a GHS-R1a secretagogue, such as a ghrelin-like compound, to increase or maintain an individual's lean body mass, preferably in combination with the treatment or prophylaxis of conditions e.g. relating to pathological weight or fat loss, including

a) prophylaxis or treatment of cachexia, and/or
b) stimulation of appetite, and/or
c) stimulation of food intake, and/or
d) stimulation of weight gain, and/or
e) increase of body fat mass and/or
f) improvement in anticancer therapy tolerability and/or
g) improvement in anticancer therapy response rate.

In particular, the present invention relates to increasing or maintaining an individual's lean body mass in combination with the treatment or prophylaxis of

cachexia and/or the stimulation of appetite, most preferably the prophylaxis or treatment of cachexia.

In a second aspect, the present invention is directed to the treatment of individuals suffering from, or at risk of suffering from, COPD. Said patient may, although not necessarily, be a lung transplant patient. Said patient may also simultaneously suffer from, or be at risk of suffering from, any of the conditions listed above, such as e.g. cachexia. In one embodiment, the individual suffering from COPD also benefits from an increased or maintained lean body mass, as described elsewhere herein, after administration of the secretagogue compound as described herein.

Facilitating a weight gain or facilitating maintenance of weight in an individual suffering from COPD, in particular in individuals suffering from a pathological weight loss, is not only a matter of stimulating appetite and/or food intake but rather correcting the imbalance between energy intake and energy consumption, i.e. total body metabolism. However, some individuals will still benefit from stimulation of appetite, particularly those individuals for whom a pathological process has led to a lowered appetite, which will naturally lead to an unhealthy weight loss. Thus, in one aspect the present invention relates to the stimulation of appetite by administering a secretagogue, such as a ghrelin-like compound. The stimulation of appetite may be measured using for instance a visual analog scale for measuring appetite, feeling of hunger or satiety level as described in the Examples. In a preferred embodiment of the invention, the stimulation is at least 5% compared to prior to the treatment, such as 10% higher, more preferably 20% higher or even more preferably 30%, 40% or 50% higher.

Stimulation of appetite does not necessarily lead to an increase in food intake, and accordingly, the present invention further relates to another aspect: the stimulation of food intake by administering a secretagogue, such as a ghrelin-like compound. The food intake can be measured using a multitude of techniques including self-reporting using e.g. diaries or questionnaires, measurements of calorie-intake from a buffet meal, using weighing of food prior to ingestion, or weighing and analysis of paired quantities of food. The food intake may be measured on a meal basis, a daily basis, a weekly basis or a monthly basis. In a preferred embodiment of the invention, the treatment results in at least a 1% increase in food intake, such as an

increase of at least 2%, more preferably at least 3%, or at least 5% or at least 7%, and even more preferred at least 10% above average food intake prior to initiation of treatment. In another embodiment, the treatment leads to increase in calorie intake irrespective of changes in food intake, since amount of food ingested may not be directly related to the ingested calorie intake, as the various food items such as fat, carbohydrates and proteins, contain different amounts of calories per amount food. In a preferred embodiment of the invention, the treatment results in at least a 1% increase in calorie intake, such as an increase of at least 2%, more preferably at least 3%, or at least 5% or at least 7%, and even more preferred at least 10% in calorie intake.

Thus, in one embodiment, the present invention relates to stimulation of weight gain or maintaining a stable body-weight by administering a secretagogue, such as a ghrelin-like compound, to an individual suffering from, or at risk of suffering from, COPD. Thus, preferably, the secretagogue, such as a ghrelin-like compound, is useful for stimulating food intake and weight gain, more preferably the secretagogue, such as a ghrelin-like compound, is useful for stimulating weight gain or for maintaining stable body weight.

It is preferred that the secretagogue, such as a ghrelin-like compound, is administered prior to a meal, such as within 180 minutes prior to a meal, such as within 150 minutes prior to a meal, for example within 120 minutes prior to a meal, such as within 100 minutes prior to a meal, for example within 80 minutes prior to a meal, such as within 60 minutes prior to a meal, for example within 45 minutes prior to a meal, such as within 30 minutes prior to a meal, for example within 15 minutes prior to a meal.

In particular the present invention is useful for treatment of under weight subjects, or for preventing loss of weight to a stage of under weight. Under weight subjects include those having a body weight about 3%, 5% or less, 10% or less, 20% or less, or 30% or less, than the lower end of "normal" weight range or Body Mass Index ("BMI")."Normal" weight ranges are well known in the art and take into account factors such as a patient age, height, and body type. Furthermore, the invention is suitable for treating patients who have experienced an involuntary weight-loss prior

to commencement of treatment, such as a weight-loss of 1% per month, 2% or less per month, or 5% or less per 6 months.

An increase in the body fat mass of an individual can be readily assessed by the skilled person using a number of state of the art techniques. In one embodiment the invention relates to an increase in body fat mass without the individual gaining weight overall. A preferred embodiment of the invention leads to an increase in body fat of at least 2% compared to prior to the initiation of treatment, more preferably at least 4%, such as at least 5%, and at least 8% and at least 10 %, even more preferably at least 20% or at least 40% above pre-treatment values.

To obtain any of the above-mentioned effects, only one GHS-R1a secretagogue need be administered if it is given in a sufficient dosage to cause all the required effects (for example, increase or maintenance of lean body mass together with the required secondary effects), such as a dosage comprising an amount of the secretagogue or a salt thereof equivalent to from 0.3 μg to 600 mg ghrelin.

However, it may also be desirable in some embodiments to administer at least two GHS-R1a secretagogues to obtain an additive or synergistic effect, such as by using at least three secretagogues. This could for instance be a non-peptide (e.g. small molecule) secretagogue in combination with a peptide secretagogue, providing both constant stimulation of the GHS receptor as well as peak stimulation in association with meal(s).

It is furthermore envisaged that administration of a GHS-R1a secretagogue may be used as part of the "supportive care regimen" for treatment of a patient in need thereof, e.g. to encourage intake of food and/or counteract any metabolic changes caused by the patient's state and/or therapy, and/or increase the patients functional status and/or increase the patient's life quality. Such patients in need thereof include, but are not restricted to, cancer patients, transplant patients (both before and after transplant) and patients having undergone, or who are going to undergo, a major operative procedure. In one preferred embodiment, said GHS-R1a secretagogue is administered as supportive care to optimise nutritional status in a patient preparing to undergo, undergoing or having undergone an anorectic therapy, such as cytoxic therapy, such as cytotoxic chemotherapy, more preferably acting to

increase or maintain lean body mass. In one embodiment, the administration of a GHS-R1a secretagogue as part of a supportive care regimen may be started up to a month before, such as two weeks before, for example a week before, the primary treatment (such as anorectic therapy or major operation) is due to start, with the GHS-R1a secretagogue being administered e.g. 1-2 times daily.

As part of the above-mentioned supportive care regime to increase an individual's nutritional status, it is envisaged that, in one embodiment, the GHS-R1a secretagogue administration acts to counteract loss of lean body mass, such as acting to increase the individual's lean body mass, and/or increasing the individual's percentage lean body mass.

In one preferred embodiment of the present invention, the individual treated for is elderly, such as 60-120 years old, more preferably 70-120 years old, such as 80-120 years old, for instance 90-120 years old. Equally preferably, said individual is a child, such as from 0-20 years old, for example 0-15 years old, such as 0-10 years old, for example 0-5 years old, such as 0-1 years old, such as a newborn child less than 2 months old.

The present inventors have found that it is possible to obtain a sufficient effect of a GHS-R1a secretagogue when administered subcutaneously, in particular when administered subcutaneously prior to a meal, thereby ensuring a close mimic of the natural pre-meal situation.

Effects of treatment with a GHS-R1 secretagogue in combination with increasing or maintaining the lean body mass of an individual

In addition to increasing or maintaining lean body mass, it is also envisaged that treatment with a GHS-R1A secretagogue will have other (interrelated or separate) positive effects on the physiological state of the individual thus treated. These additional treatment effects, which occur in addition to the increase or maintenance of lean body mass, more preferably percentage increase in lean body mass, are detailed below:

Thus, in addition to the effect of the secretagogue in increasing or maintaining lean body mass, the GHS-R1A secretagogue may be given in an amount effective to prevent and/or treat cachexia/malnutrition or to maintain metabolic homeostasis in patients.

Cachexia, or wasting, is one of the most distressing and devastating symptoms of several severe diseases, robbing people of their energy, sense of well-being, and quality of life, and increasing their dependence on others.

The foremost sign of cachexia is weight loss, not only of fatty tissue but also of muscle tissue and even bone. This non-fatty tissue is also known as "lean body mass." In addition, there is loss of appetite (anorexia), weakness (asthenia), and a drop in hemoglobin level (anemia).

Treatment of cachexia is not simply a matter of eating more. Even if the person wants to eat, even if he or she tries to eat, even if the person is given nutrients through a stomach tube or intravenously, the condition will normally not be reversed. Cachexia, or wasting, as it may also be called is seen with several diseases, such as AIDS, cancer, post hip fracture, chronic heart failure, chronic lung disease, such as COLD, COPD, liver cirrhosis, renal failure, and autoimmune diseases such as rheumatoid arthritis and systemic lupus, sepsis and severe infection. Furthermore, wasting is also seen in aging. Cachexia is found as the terminal state of many different clinical conditions or in chronic diseases such as cancer, infections, AIDS, congestive heart failure, rheumatoid arthritis, tuberculosis, post-hip fracture, cystic fibrosis and Crohn's disease. It can also occur in elderly people who do not have any obvious symptoms of disease. Although cachexia represents the complex metabolic syndrome that is seen in such patients it is commonly recognized as a progressive weight loss with depletion of host reserves of adipose tissue and skeletal muscle.

Cancer may cause cachexia through a variety of mechanisms, including induction of anorexia and/or increase or change of metabolism. Energy intake has been shown to be substantially reduced among weight-loosing cancer patients. Cancer patients may frequently suffer from physical obstruction of the GI tract, pain, depression, constipation, malabsorption, debility or the side effects of treatment such as opiates, radiotherapy or chemotherapy, which all may decrease food intake (Barber, Ross,

and Fearon 133-41). Cancer associated hypercalcemia may also induce nausea, vomiting and appetite loss.

The central mechanism of cancer-induced anorexia and cachexia is complex and includes many different mediators. Recent research has revealed that the condition mainly is caused by the body's reaction to the presence of the underlying disease leading to alterations in the neuro-endocrine system, to the production of a variety of pro-inflammatory cytokines. Recent research also indicates that, in some cases, tumors themselves produce substances that induce cachexia. and to the release of cancer specific cachectic factors. In turn, these mediators cause either a reduction in food intake, abnormality in the metabolism or a combination of these two. Cancer cachexia may be induced or aggravated by anticancer therapies, such as chemotherapy or radiation therapy, which are associated with a high incidence of anorexia and nausea.

Cancer cachexia is reported to occur in about half of all cancer patients and is associated with more than 20 percent of cancer deaths (Tisdale MJ. Nat Rev Cancer 2002, 2:862871). The condition often occurs during advanced cancer, in particular when metastatic tumours are present in the body. Cachexia is also more common in children and elderly patients

Specific cancers are also consistently identified where the frequency of cancer cachexia is particularly high:

- Upper GI cancers (including: pancreas, stomach, oesophagus, and liver) (Bruera E. BMJ 1997;315:1219-1222.(8 November); (Palesty JA et al. Dig Dis 2003;21:198-213)
- Lung cancer (www.oxandrin .com), in particular small cell lung cancer
- Head and neck cancer (www.oxandrin.com)
- Colorectal cancer
- Other solid tumours (Bruera E. BMJ 1997;315:1219-1222.(8 November)

For example, the Oxandrin website (www.oxandrin.com) states that 'In an Eastern Cooperative Oncology Group (ECOG) study addressing the impact of weight loss in advanced cancer, IWL (involuntary weight loss) was associated with an approximate 50% drop in survival and decreased tolerance of cancer therapy. Cancer sites

associated with the greatest risks for weight loss are those affecting the aerodigestive tract (lung, head and neck, and esophagus) and the gastrointestinal system, especially pancreas, stomach, and liver.'

Furthermore, at the moment of diagnosis, 80% of all patients with cancer in upper GI tract and 60 % of all patients with lung cancer have already experienced substantial weight loss (Bruera 1219-22). On average, the prevalence of cachexia increases from 50 percent to more than 80% percent before death and in more than 20 % of the patients cachexia is the main cause of death (Bruera 1219-22).

Detection of cancer cachexia: The nutritional state is evaluated with a combination of clinical assessment, antropometric tests (body weight, skin fold thickness and mid arm circumference) and imaging (DEXA scan, MR scan, CT scan and bioelectric impedance meassuring). Cachexia is generally suspected if the involuntary weight loss of greater than 5% of the premorbid weight is observed within a six-month periode – especially when combined with muscle wasting.

The most commonly used laboratory parameter is serum albumin. It is however an unspecific parameter. Other markers are proteins with a short half life transferrrin and transthyretin has also been used.
Other markers of canchexia are IGF-1, IGFBP-3, ALP (alkaline phosphatase) and testosterone.

In particular the GHS-R1A secretagogue may be used to increase or maintain an individual's lean body mass in combination with the prevention and/or treatment of cachexia or malnutrition in individuals suffering from any of the following:

- Cancer
- AIDS
- Cardiac failure
- Pulmonary insufficiency due to for instance COPD, pulmonary fibrosis, cystic fibrosis or alpha 1-antitrypsin deficiency
- Renal failure due to for instance glomerulonephritis, tubulointerstitial nephropathy, hereditary nephropathy (e.g.

polycystic kidney disease), hypertension, diabetes mellitus, vascular disease, obstructive uropathy

- Liver failure due to for instance viral hepatitis, toxic hepatitis, fibrosis, cirrhosis, primary biliary cirrhosis, hereditary liver diseases
- Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus
- Severe chronic infections such as tuberculosis

In another preferred embodiment, the GHS-R1A secretagogue may be used to increase or maintain an individual's lean body mass in combination with the prevention and/or treatment of cachexia or malnutrition in any of the following conditions:

- Organ transplantation patients
- Patients undergoing or recovering from major surgery
- Patients recovering from trauma, such as especially trauma requiring surgical intervention
- Premature children and children born small for gestational age
- Critical illness
- Severe infections such as sepsis
- Severe burns
- Major trauma
- Major surgery such as cardiothoracic surgery, transplantation
- Treatment with catabolic agents such as glucocorticoids
- frailty in elderly persons
- heart failure, such as due to ischaemic heart disease, cardiomyopathy, hypertension, valvular dysfunction or heart failure due to pulmonary disease such as chronic bronchitis, pulmonary hypertension, emphysema or heart failure caused by genetic defects
- tissue ischaemia, such as cardiac ischaemia due to for instance coronary artery disease, or cerebral ischaemia due to thrombo-embolism
- bone and cartilage related diseases, such as osteoporosis
- treatment of bone fractures, by acceleration of fracture healing and recovery following major fractures

- inflammatory diseases, such as inflammatory bowel diseases
- malignant diseases, such as breast cancer and thyroid cancer
- treatment of hyperthyroidism, e.g. for preventing weight gain in individuals being converted from a hyperthyroidic state to euthyroid state
- sleeping disorders

The GHS-R1A secretagogues will also improve the nutritional condition of the individuals being treated due to an increase of gastric motility and gastric emptying. Accordingly, the GHS-R1A secretagogue may be used in the treatment or prevention of delayed gastric emptying/gastroparesis, such as in patients with diabetes mellitus, patients with renal failure patients with liver failure, patients with idiopathic gastroparesis, critically ill patients, patients undergoing anaestesia and patients undergoing surgery.

Furthermore, the GHS-R1A secretagogues may be used for prevention and treatment of postoperative ileus.

Further indications suitable for being treated with a GHS-R1a secretagogue according to the present invention are any indications commonly associated with cachexia, such as any of the following groups of pathological conditions:

1) Any condition associated with increased metabolism and catabolism of protein and/or fat tissue, such as inflammation, infection, fever, trauma or neoplasma.

2) Any gastro-intestinal condition characterized by mal-digestion and/or mal-absorption.

3) Conditions associated with excessive energy loss e.g nefrotic syndrome, serious burns and diabetes mellitus.

4) Pulmonary diseases such as COPD, pulmonary infections (bacterial, viral, pneumocystis etc), Asthma or hypersensitivity pneumonits.

5) Kidney diseases such as chronic renal failure, glomerulonephephritis, diabetes, hypertension, and cystic kidney diseases, urinary tract infections or obstruction induced kidney dysfunction or Nephrolithiasis.

6) Gastro-intestinal diseases such as motility related disorders, Gastritis, oesophagitis, liver and biliary diseases (e.g. cholangitis and extrahepatic biliary obstruction) with decreased absorption, Crohn's diseases, ulcerative colitis, enteritis or diverticulosis.

7) Liver diseases such as hepatitis (e.g. viral, drug induced, toxic and ischemic), Cirrhosis (e.g. alcoholic, postnecrotic, biliary, hemochromatosis), infiltration (glycogen, fat amyloid, lymphoma and granuloma), Vascular caused, decreased liver function.

8) Pancreatitis

9) Immunological diseases such as Immunodeficiency (e.g. acquired AIDS and inherited), allergies, Autoimmunity diseases (e.g. rheumatoid arthritis, systemic sclerosis, vasculitis syndromes, systemic lupus erythematosus), T- and B-cell neoplasma

10) Endocrine dysfunction, such as Diabetes mellitus or hyperthyroid states

11) Post surgery and post fracture

12) Neurological condition: Multiple sclerosis, Alzheimer and other primary dementias,

13) Cancer patients – including any of the indications described herein; also including any of the neoplastic diseases described in PCT patent application PCT/DK2004/000519 (Gastrotech Pharma), incorporated herein by reference.

14) Infections, such as Osteomyolitis, pelvic inflammatory diseases, pyelonephritis, endocarditis or chronic skin infection.

The rationale for using secretagogues in the treatment of cancer cachexia

In one preferred embodiment of the present invention, the GHS-R1a secretagogue is used to increase or maintain lean body mass in an individual suffering from cancer cachexia, and the secretagogue also acts synergistically to treat the cancer cachexia itself.

Without being bound by theory, the rationale for the treatment of cancer cachexia with a GHS-R1a secretagogue, in particular a ghrelin-like compound, is based on the following:

Ghrelin released from the endocrine cells in the mucosa of the GI tract may act both locally as a paracrine substance and centrally as a hormone. Locally, ghrelin may act as an initiator of afferent activity in for example afferent vagal neurons. Such neurons will relay the ghrelin stimulus to centers in the CNS such as the nucleus tractus solitarirus (NTS) which further communicate with appetite and energy homeostasis regulatory centers such as the paraventricular nucleus and arcuate

nucleus in the hypothalamus. As a hormone, ghrelin is believed to act on central appetite regulating POMC and NPY/AGRP neurons, which express ghrelin receptors. Most of these neurones in the arcuate nucleus as such are located inside the blood brain barrier and is consequently not accessible to blood born messengers such as ghrelin. However, some POMC and NPY/AGRP neurons are found in the nearby median eminence, a cicumventricular organ, which is clearly outside the blood brain barrier and are therefore target for hormonally transmitted ghrelin signaling from the GI tract. However, recently it has been described that ghrelin is transported across the blood brain barrier (Banks et al. 822-27). It is important to note that at the central appetite regulatory center, for example at the NPY / AGRP neurons – i.e. the first level neurons in the stimulatory branch of appetite control – ghrelin acting through stimulatory ghrelin receptors is the only stimulatory input known from the periphery. All other hormones and neurotransmitters: leptin, insulin, PYY3-36, a-MSH etc. act as inhibitors on the NPY/AGRP neurons in this important "appetite gate-keeping" center. Since the NPY system in down-regulated during cancer induced cachexia ghrelin stimulation of this system may be able to normalize the condition. Similarly the melanocortin that is active during cancer induced cachexia, may be inhibited by Ghrelin through stimulation of AgRP.

Increase in ghrelin has also been shown to increase ATCH with a resulting increase in cortisol level. This action may have important beneficial implications for the treatment of cachexia, as cortisol decreases the level of cytokines (IL-1β, IL-6, TNF-α, IFN-α). Administration of glucocorticoids is already widely used in the palliative setting for symptoms associated with cancer (Inui 72-91)

Furthermore, it is known that ICV injection of ghrelin has been shown to decrease core body temperature in rodents, which indicates a decrease in the REE (Lawrence CB, Endocrinology. 2002 Jan;143(1):155-62). Again without being bound by theory it is expected that ghrelin will revert the increase in REE which is an important feature of the cachexia as described above.

The GHS-R1a secretagogue, in particular a ghrelin-like compound, may be administered using any suitable regimen taking into account the knowledge of the expected cancer progress as well as the anti-neoplastic therapy regime.

In one embodiment, it is envisaged that, according to the present invention, a GHS-R1a secretagogue can be administered to any individual suffering from any cancer type, regardless of etiology, to successfully treat, reduce or prevent cancer cachexia, in combination with increasing or maintaining said individual's lean body mass. Thus, in one preferred embodiment of the present invention, the treatment of an individual with a GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, is for the treatment or prevention of cancer cachexia caused by any of the cancer types described on p21-27 of PCT/DK2004/000519 (Gastrotech Pharma), incorporated herein by reference.

As discussed above cancer cachexia may be due to a catabolic disorder, i.e. a hypermetabolic state as described above, either resulting from the progressive tumor growth or from the catabolic side effects of the anti-cancer therapy. However, the cancer cachexia may also be due to an anorectic disorder, such as is the case when the individual suffering from the cancer has no appetite or the position of the tumor reduces food intake.

Accordingly, in one embodiment of the invention the treatment with a GHS-R1a secretagogue, such as a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with the treatment or prevention of cancer cachexia caused by a catabolic disorder. This is particularly suitable when the cancer is a GI tract cancer, especially a upper GI tract cancer (it is to be understood herein that the term "upper GI tract cancer" also encompasses pancreatic cancer), lung cancer, in particular small cell lung cancer, liver cancer (it is to be understood herein that the term "liver cancer" also encompasses metastatic cancer processes in the liver).

In another embodiment of the invention the treatment with a GHS-R1a secretagogue, such as a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with the treatment or prevention of cancer cachexia caused by an anorectic disorder.

In yet another embodiment the treatment with a GHS-R1a secretagogue, such as a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with the treatment or prevention of cancer cachexia independent of how

the cancer has induced the cachexia, as well as for cachexia caused by a combination of the catabolic disorder and the anorectic disorder.

In another preferred embodiment of the present invention, the treatment with a GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with treatment or prevention of cancer cachexia caused by a solid tumour.

Another sub-group of cancers are those with anorexia caused by dysregulation of the central appetite regulatory centre in hypothalamus, where other possible reasons to eat less are excluded. In particular individuals in terminal cancer states where further cancer treatment is impossible would benefit from ghrelin treatment as a palliative treatment to increase food intake, improve the digestion and metabolism.

Accordingly, a third aspect of the invention relates to use of a GHS-R1a secretagogue to increase or maintain an individual's lean body mass in combination with the palliative treatment of terminal cancer states in an individual in need thereof, such as wherein said individual is suffering from advanced-stage cancer, preferably terminal cancer.

In accordance with the above, the invention is particularly suitable for treating or preventing cachexia in an individual suffering from the following aerodigestive tract cancer forms:

- Pancreatic cancer
- cancer of the upper GI tract, such as stomach cancer and/or esophagus cancer.
- head and neck cancer, in particular cancer of the thyroid or cancer of the salivary glands.
- lung cancer, in particular small lung cell cancer.

In another preferred embodiment of the present invention, the treatment with a GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with the treatment or prevention of cancer cachexia caused by lower GI cancer, such as colorectal cancers, in particular by colon cancer.

In another preferred embodiment of the present invention, the treatment with a GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with treatment or prevention of cancer cachexia caused by an endocrine cancer, i.e. a cancer in an endocrine organ of an individual's body.

The invention is also useful for treating individuals suffering from the following cancer forms:

- cancer of the ovaries
- breast cancer.

In a further preferred embodiment of the present invention, the treatment with a GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with treatment or prevention of cancer cachexia caused in whole or in part by anti-cancer treatment, such as chemotherapy or radiotherapy or combinations thereof.

In another embodiment of the present invention, the treatment with a GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, is to increase or maintain an individual's lean body mass in combination with improvement of anticancer therapy tolerability or an improvement in anticancer therapy response rate.

In one embodiment it is preferred that the GHS-R1a secretagogue, such as a ghrelin-like compound, is administered prophylactically for preventing or delaying a cachectic state. In this embodiment the treatment may be started before any anti-neoplastic treatment initiates. It may be administered continuously during the anti-neoplastic treatment or it may be administered at intervals, for example between periods with anti-neoplastic therapy. By administering during and in particular between the periods of anti-neoplastic therapy, the risk that the treated individual acquires infections and other complications may be reduced due to the better health conditions.

Treatment of cancer cachexia using a GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, may be achieved using any administration method known in

the art. Preferably, it may be achieved using any of the administration methods described herein, more preferably using i.v. or subcutaneous administration, most preferably using subcutaneous administration methods.

Stimulation of appetite, food intake, weight gain, increase of body fat mass

In all aspects of the present invention, the GHS-R1 secretagogue can for example be given in an amount effective to stimulate appetite and/or food intake and/or weight gain and /or increase of body fat mass.

As written above, facilitating a weight gain or facilitating maintenance of weight, in particular in individuals suffering from a pathologically weight loss, is not only a matter of stimulating appetite and/or food intake but rather correcting the imbalance between energy intake and energy consumption, i.e. total body metabolism.

However, some individuals will still benefit from stimulation of appetite, particularly those individuals for whom a pathological process has led to a lowered appetite, which will naturally lead to an unhealthy weight loss. Thus, in one aspect the present invention relates to increasing or maintaining an individual's lean body mass in combination with the stimulation of appetite, by administering a GHS-R1a secretagogue, such as a ghrelin-like compound. The stimulation of appetite may be measured using for instance a visual analog scale for measuring appetite, feeling of hunger or satiety level. In a preferred embodiment of the invention, the stimulation is at least 5% compared to prior to the treatment, such as 10% higher, more preferably 20% higher or even more preferably 30%, 40% or 50% higher.

Stimulation of appetite does not necessarily lead to an increase in food intake, and accordingly, the present invention further relates to another aspect: increasing or maintaining an individual's lean body mass in combination with the stimulation of food intake, by administering a GHS-R1a secretagogue, such as a ghrelin-like compound. The food intake can be measured using a multitude of techniques including self-reporting using e.g. diaries or questionnaires, measurements of calorie-intake from a buffet meal, using weighing of food prior to ingestion, or weighing and analysis of paired quantities of food. The food intake may be measured on a meal basis, a daily basis, a weekly basis or a monthly basis. In a

preferred embodiment of the invention, the treatment results in a 1% increase in food intake, such as an increase of 2%, more preferably 3%, or 5% or 7%, and even more preferred 10% above average food intake prior to initiation of treatment. In another embodiment, the treatment leads to increase in calorie intake irrespective of changes in food intake, since amount of food ingested may not be directly related to the ingested calorie intake, as the various food items such as fat, carbohydrates and proteins, contain different amounts of calories per amount food. In a preferred embodiment of the invention, the treatment results in a 1% increase in calorie intake, such as an increase of 2%, more preferably 3%, or 5% or 7%, and even more preferred 10% in calorie intake.

In a third aspect the present invention relates to increasing or maintaining an individual's lean body mass in combination with stimulation of weight gain or maintaining a stable body-weight, by administering a GHS-R1a secretagogue, such as a ghrelin-like compound.

Preferably the GHS-R1a secretagogue, such as a ghrelin-like compound, is useful for stimulating food intake and weight gain, more preferably the secretagogue, such as a ghrelin-like compound, is useful for stimulating weight gain or for maintaining stable body weight.

As discussed below it is preferred that the GHS-R1a secretagogue, such as a ghrelin-like compound, is administered prior to a meal, such as within 180 minutes prior to a meal, such as within 150 minutes prior to a meal, for example within 120 minutes prior to a meal, such as within 100 minutes prior to a meal, for example within 80 minutes prior to a meal, such as within 60 minutes prior to a meal, for example within 45 minutes prior to a meal, such as within 30 minutes prior to a meal, for example within 15 minutes prior to a meal. Furthermore, it is preferred that the ghrelin-like compound is administered subcutaneously.

Furthermore, a GHS-R1a secretagogue, such as a ghrelin-like compound may be administered to increase or maintain an individual's lean body mass in combination with facilitating maintenance of physical functioning, and/or facilitating recovery of physical function, for example in individuals recovering from major surgeries, such as insertion of a hip prosthesis, amputations, and bone fractures.

In particular the present invention is useful for treatment of under weight subjects, or for preventing loss of weight to a stage of being underweight. Under weight subjects include those having a body weight about 3%, 5% or less, 10% or less, 20% or less, or 30% or less, than the lower end of "normal" weight range or Body Mass Index ("BMI")."Normal" weight ranges are well known in the art and take into account factors such as a patient age, height, and body type. Furthermore, the invention is suitable for treating patients who have experienced an involuntary weight-loss prior to commencement of treatment, such as a weight-loss of 1% per month, 2% or less per month, or 5% or less per 6 months.

Increasing weight or appetite can be useful for a patient having a disease or undergoing treatment that affects weight or appetite. In addition, for example, farm animals such as pigs, cows and chickens can be treated to gain weight.

An increase in the body fat mass of an individual can be readily assessed by the skilled person using a number of state of the art techniques. Further conditions of in individual capable of being treatable in accordance with the present invention are bulimia nervosa, anorexia, male erectile dysfunction, female sexual dysfunction, amelioration of ischemic nerve or muscle damage, as well as systemic lupus erythematosus.

Quality of Life

In all aspects of the present invention, it is preferred that the treatment method and/or pharmaceutical compositions and/or compounds of the present invention are capable of affording the individual thus treated an improved quality of life (QOL), for example as is caused by improved appetite and/or body weight and/or nutritional status and/or increased or maintained lean body mass. Thus, in one aspect the invention relates to improvements of Quality of Life using a secretagogue, such as ghrelin or a ghrelin-like compound as described herein. In another embodiment, said improvement in an individual's life quality is assessed using a "Quality of life" questionnaire, as is known to one skilled in the art.

Two validated quality of life surveys preferred for use in assessing improved quality of life as caused by the administration of the compounds of the present invention are as follows:

(i) Medical Outcomes Study Short-Form Health Survey (SF-36). The SF-36 contains 36 questions that assess eight aspects of the patients' QOL; physical functioning (PF), role-physical functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional functioning (RE), and mental health (MH). According to the manual and interpretation guide responses to questions within scales are summed and linearly transformed to scale scores that range from 0, representing poor health status, to 100, representing optimal health status. The Swedish version has been validated and normative data have been presented for the general Swedish population (Sullivan MKJ, Ware J. Hälsoenkät: svensk manual och tolkningsguide (SF-36 Health Survey. Swedish manual and interpretation guide). Göteborg: Sahlgrenska University Hospital; 1994.)

(ii) EORTC QLQ-C30 (+3) questionnaire. The EORTC QLQ-C30 (version 1.0) is a 30 item core questionnaire intended for assessment of QOL among patients, the instrument is developed by the EORTC Quality of Life Study group. The first version has been validated in cancer patients and reference data from general populations have been published. The questionnaire comprises five functional scales; physical functioning (five questions), role functioning (two questions), emotional functioning (four questions), cognitive functioning (two questions) and social functioning (two questions). There are three symptom scales; fatigue (three questions), nausea and vomiting (two questions) and pain (two questions), and there are six single items on dyspnoea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties. Two global questions are asking about the patient's health status and overall QOL. All scales and single-items measures range in score from 0 to 100. A high score for the functioning scales and the global health status and QOL represents a high level of functioning / health status and QOL. A high score for the symptom / item scales represents a high level of symptoms / problems. The QOL scores can be calculated according to the EORTC QLQ-C 30 scoring manual.

Preferred questionnaires for assessing a patient's improved quality of life after treatment with one or more secretagogue compounds are given in Example 8 of published patent application WO 2005/014032 (Gastrotech Pharma: "Use of

secretagogues like ghrelin in cancer cachexia and for stimulating appetite"): Examples of questionnaires assessing patient quality of life:

A) EORTC QLQ-C30

B) Taste questionnaire

C) Hunger-Appetite-Feeling of Supersaturation-Nausea-Anxiety-Tiredness – Visual analogue scale

In preferred embodiments of the present invention, treatment of patients with the described conditions results in a significant improvement in the patient's quality of life. Preferably, the treatment results in a significant increase in quality of life as measured using any method for testing the quality of life including, but not limited to, the above mentioned questionnaires, e.g. an increase in the quality of life score(s), or a composite quality of life score, as appropriate for the individual measuring tool, or a decrease in score(s) related to the symptoms and/or problems, respectively. This increase or decrease, respectively, is preferably 1% above the score obtained prior to initiation of the treatment, more preferably 2% above, even more preferred 5%, such as 10%, even more preferred 20%, 50% or 75% above the pre-treatment score. In another embodiment, the treatment results in measurable increases in quality of life score such that the score after treatment is equal to the average score found in a comparable healthy subject pool, or close to such a "normal" score, i.e. more than 50% of the score, even more preferably 60% of the score, or more preferably 75% of the score. Further, in another embodiment, the treatment results in a decrease in the score(s) related to the symptoms and/or problems of at least 1%, more preferably 3%, even more preferably 5% or more preferred 10%, 20%, 30% or 50% of the score(s) prior to initiation of treatment. These increases or reductions, respectively, may refer to one, several, or all of the aspects of the individual quality of life measuring tool, or a composite score when appropriate.

Ghrelin-like compound

Any GHS-R1A secretagogue, such as ghrelin or a ghrelin-like compound, may be used in the present invention. One preferred type of ghrelin-like compound according to the invention described herein is a compound comprising a structure defined by formula I:

Formula I: $Z^1 - (X^1)_m - (X^2) - (X^3)_n - Z^2$, wherein

Z^1 is an optionally present protecting group

each X^1 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

X^2 is any amino acid selected from naturally occurring and synthetic occurring amino acids, said amino acid being modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

each X^3 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

wherein one or more of X^1 and X^3 optionally may be modified by a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

Z^2 is an optionally present protecting group,

m is an integer in the range of from 1-10

n is 0 or an integer in the range of from 1-35.

Accordingly, the term "secretagogue" or "growth hormone secretagogue", or "GHS-R1a secretagogue" includes the naturally occurring 28 aa human ghrelin, the amino acid of which is shown in SEQ ID NO: 1, as well as the naturally occurring 27 aa human ghrelin, the amino acid of which is shown in SEQ ID NO: 2. Thus, the present invention relates to the use of ghrelin or a peptide homologous thereto. Ghrelin is described by Kojima in Nature (1999), vol. 402,656-660.

The present invention includes diastereomers as well as their racemic and resolved enantiomerically pure forms. GHS-R1a secretagogues can contain D-amino acids, L-amino acids, alpha-amino acid, beta-amino acid, gamma-amino acid, natural amino acid and synthetic amino acid or the like or a combination thereof. Preferably, amino acids present in a ghrelin-like compound are the L-enantiomer.

Further suitable GHS-R1a secretagogues for use in the present invention are disclosed in PCT patent application no. PCT/DK2004/000529, Danish patent application no. PA 200401875, and PCT applications with publication numbers WO0192292 (Merck and Co. Inc), WO0134593 (Novo Nordisk AS) and WO0107475 ("Novel peptides", Kangawa et al.); said documents all being incorporated herein by reference.

Methods for production of GHS-R1a secretagogues are well known to those skilled in the art, for example in Example 2 of PCT patent application PCT/DK2004/000519 (Gastrotech Pharma), incorporated herein by reference. Techniques for chemical synthesis of polypeptides are well known in the art. (See e. g., Vincent in Peptide and Protein Drug Delivery, New York, N. Y., Dekker, 1990.) Examples of techniques for biochemical synthesis involving the introduction of a nucleic acid into a cell and expression of nucleic acids are provided in Ausubel, Current Protocols in Molecular Biology, John Wiley, 1987-1998, and Sambrook et al., in Molecular Cloning, A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989.

Functionality

The GHS-R1a secretagogues described herein, in particular ghrelin-like compounds, are active at the receptor for GHS as described above, i.e. the receptor GHS-R 1a. The compounds can bind to the receptor, and preferably, stimulate receptor activity.

The receptor activity can be measured using different techniques such as detecting a change in the intracellular conformation of the receptor, in the G-protein coupled activities, and/or in the intracellular messengers.

One simple measure of the ability of a GHS-R 1a secretagogue to activate the ghrelin receptor is to measure its EC50, i.e. the dose at which the compound is able to activate the signalling of the receptor to half of the maximal effect of the compound.

The receptor can either be expressed endogenously on primary cells cultures, for example pituitary cells, or heterologously expressed on cells transfected with the

ghrelin receptor. Whole cell assays or assays using membranes prepared form either of these cell types can be used depending on the type of assay.

As the receptor is generally believed to be primarily coupled to the Gq signalling pathway, any suitable assay which monitor activity in the Gq/G11 signalling pathway can be used, for example:

1) an assay measuring the activation of Gq / G11 performed for example by measurement of GTPgS binding combined with, e.g., anti-G-alpha-q or -11 antibody precipitation in order to increase the signal to noise ratio. This assay may also detect coupling to other G-proteins than Gq/11.

2) An assay which measure the activity of phopholipase C (PLC) one of the first down-stream effector molecules in the pathway, for example by measuring the accumulation of inositol phosphate which is one of the products of PLC.

3) More down stream in the signalling cascade is the mobilization of calcium from the intracellular stores

4) Further more down stream signalling molecules such as the activity of different kinds of MAP kinases (p38, jun, ect.), NF-κ-B translocation and CRE driven gene transcription may also be measured.

5) Binding of fluorescently tagged arrestin to the activated ghrelin receptor

Other examples of suitable protocols for use in determining secretagogue functionality are given in Example 5 of published patent application WO 2005/014032 (Gastrotech Pharma: "Use of secretagogues like ghrelin in cancer cachexia and for stimulating appetite"): *Functional tests on the ghrelin receptor*

In one embodiment the binding of a compound to the receptor GHS-R 1A can be measured by the use of the assay described herein above.

A GHS-R 1a secretagogue according to the invention preferably has at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about

90%, functional activity relative to 28 aa human ghrelin as determined using the assay described herein above, and/or an EC50 greater than about 1,000, greater than about 100, or greater than about 50, or greater than about 10. Greater refers to potency and thus indicates a lesser amount is needed to achieve binding inhibition.

In one embodiment of the invention, the compound has a potency (EC50) on the GHS-R 1A of less than 500 nM. In another embodiment the compound has a potency (EC50) on the GHS-R 1A of less than 100 nM, such as less than 80 nM, for example less than 60 nM, such as less than 40 nM, for example less than 20 nM, such as less than 10 nM, for example less than 5 nM, such as less than 1 nM, for example less than 0.5 nM, such as less than 0.1 nM, for example less than 0.05 nM, such as less than 0.01 nM.

In a further embodiment the dissociation constant (Kd) of the compound is less than 500 nM. In a still further embodiment the dissociation constant (Kd) of the ligand is less than 100 nM, such as less than 80 nM, for example less than 60 nM, such as less than 40 nM, for example less than 20 nM, such as less than 10 nM, for example less than 5 nM, such as less than 1 nM, for example less than 0.5 nM, such as less than 0.1 nM, for example less than 0.05 nM, such as less than 0.01 nM.

Binding assays can be performed using recombinantly-produced receptor polypeptides present in different environments. Such environments include, for example, cell extracts and purified cell extracts containing the receptor polypeptide expressed from recombinant nucleic acid or naturally occurring nucleic acid; and also include, for example, the use of a purified GHS receptor polypeptide produced by recombinant means or from naturally occurring nucleic acid which is introduced into a different environment.

Using a recombinantly expressed GHS receptor offers several advantages such as the ability to express the receptor in a defined cell system, so that a response to a compound at the receptor can more readily be differentiated from responses at other receptors. For example, the receptor can be expressed in a cell line such as HEK 293, COS 7, and CHO not normally expressing the receptor by an expression vector, wherein the same cell line without the expression vector can act as a control.

Functionality of a GHS-R1a secretagogue may be demonstrated in mammals using e.g. the test for the absolute bioavailability of iv administered Ghrelin and sc administered Ghrelin described in Example 3 of PCT patent application PCT/DK2004/000519 (Gastrotech Pharma), or the method in Example 6 "Efficacy of subcutaneous administration of Ghrelin" from PCT patent application PCT/DK2004/000519 (Gastrotech Pharma), or the trial described in Example 11 "Administering ghrelin to cancer cachexia patients" from PCT patent application PCT/DK2004/000519 (Gastrotech Pharma). All these Examples are hereby incorporated herein by reference

Identity and homology

Homologues of ghrelin suitable for using as GHS-R1a secretagogue in the present invention are described in the section entitled "Identity and homology" in PCT patent application PCT/DK2004/000519 (Gastrotech Pharma), incorporated herein by reference.

In a preferred embodiment the GHS-R1a homologue has an amino acid sequence at least 80 % homologous to SEQ ID NO 1. More preferably the homology is at least at least 85 % homologous, such as at least 90 % homologous, such as at least 95 % homologous, for example at least 96 % homologous, such as at least 97 % homologous, such as at least 98 % homologous, for example 99 % homologous to SEQ ID NO 1.

Homologues to SEQ ID NO: 1 may also be 27 aa human ghrelin SEQ ID NO: 2, rat ghrelin SEQ ID NO: 3. Additional preferred sequences are listed in EP 1 197 496 (Kangawa). Other homologues are the variants described in EP 1197496 (Kangawa) and WO 01/92292 (Merck) and WO 01/56592 (Novo Nordisk), all incorporated herein by reference.

Bulky hydrophobic group

The bulky hydrophobic group of the GHS-R1a secretagogue to be used according to the invention is any bulky hydrophobic group capable of providing the des-acylated 28 aa human ghrelin, or an analogue thereof, with binding affinity to GHS-R 1a. Any

suitable amino acid may be modified with any suitable bulky hydrophobic group; in a preferred embodiment, a Ser residue (preferably amino acid number 3 in the amino acid chain) is modified with the bulky hydrophobic group.

When the amino acid being modified contains e.g. - OH, -SH, -NH or -NH_2 as a substituent group in a side chain thereof, a group formed by acylating such a substituent group is preferred. The mode of linkage may thus be selected from the group consisting of ester, ether, thioester, thioether, amide and carbamide.

For example, if the modified amino acid is serine, threonine, tyrosine or oxyproline, the amino acid has a hydroxyl group in the side chain. If the modified amino acid is cysteine, the amino acid has a mercapto group in the side chain. If the modified amino acid is lysine, arginine, histidine, tryptophan, proline oroxyproline, it has an amino group or imino group in the side chain.

The hydroxyl group, mercapto group, amino group and imino group described above may thus have been chemically modified. That is, the hydroxyl group or mercapto group may be etherized, esterified, thioetherified or thioesterified. The imino group may have been iminoetherified, iminothioetherified or alkylated. The amino group may have been amidated, thioamidated or carbamidated.

Further, the mercapto group may have been disulfidated, the imino group may have been amidated or thioamidated, and the amino group may have been alkylated or thiocarbamidated.

In a preferred embodiment the modified amino acid is Ser coupled through an ester linkage to the hydrophobic group.

Further preferred bulky hydrophobic groups are disclosed in PCT patent application PCT/DK2004/000519 (Gastrotech Pharma) and Danish patent application no. PA 200401875, both incorporated herein by reference.

Protecting group

The GHS-R1a secretagogue to be used according to the invention may comprise a protecting group at the N-terminus or the C-terminus or at both.

A protecting group covalently joined to the N-terminal amino group reduces the reactivity of the amino terminus under in vivo conditions. Amino protecting groups include - C1-10 alkyl, -C1-10 substituted alkyl, -C2-10 alkenyl, -C2-10 substituted alkenyl, aryl, -C1-6 alkyl aryl, -C(O)- (CH2) 1-6-COOH, -C(O)-C1-6 alkyl, -C(O)-aryl, -C (O)-O-C1-6 alkyl, or-C (O)-O-aryl. Preferably, the amino terminus protecting group is acetyl, propyl, succinyl, benzyl, benzyloxycarbonyl or tbutyloxycarbonyl.

A protecting group covalently joined to the C-terminal carboxy group reduces the reactivity of the carboxy terminus under in vivo conditions. The carboxy terminus protecting group is preferably attached to the a-carbonyl group of the last amino acid. Carboxy terminus protecting groups include amide, methylamide, and ethylamide.

Conjugates

The secretagogue, such as a ghrelin-like compound, to be used in the present invention may be provided in the form of a secretagogue conjugate, i.e. a molecule comprising the secretagogue conjugated to another entity.

The other entity may be any substance that is capable of conferring improved properties to the secretagogue, e.g. in terms of improved stability, half-life, etc. Examples of suitable entities are described in PCT patent application PCT/DK2004/000519 (Gastrotech Pharma) and Danish patent application no. PA 200401875, both incorporated herein by reference

Method for production

GHS-R1a secretagogues can be produced using techniques well known in the art. For example, a polypeptide region of a GHS-R1a secretagogue can be chemically or biochemically synthesized and modified. Techniques for chemical synthesis of polypeptides are well known in the art. (See e. g., Vincent in Peptide and Protein Drug Delivery, New York, N. Y., Dekker, 1990.) Examples of techniques for biochemical synthesis involving the introduction of a nucleic acid into a cell and expression of nucleic acids are provided in Ausubel, Current Protocols in Molecular Biology, John Wiley, 1987-1998, and Sambrook et al., in Molecular Cloning, A Laboratory Manual, 2 d Edition, Cold Spring Harbor Laboratory Press, 1989.

Pharmaceutical composition

While it is possible for a GHS-R 1a secretagogue or salt thereof to be administered as the raw chemical, it is preferred to present it in the form of a pharmaceutical composition. Accordingly, in one aspect the present invention relates to a pharmaceutical composition comprising a GHS-R1A secretagogue (or pharmaceutically acceptable salt thereof) suitable for use in the present invention. The pharmaceutical composition preferably comprises a pharmaceutically acceptable carrier, vehicle and/or excipient. The carrier, vehicle and/or excipient should be compatible with the GHS-R 1a secretagogue or salt thereof. In a preferred embodiment, the pharmaceutical composition is not immunogenic when administered to a human in accordance with the present invention.

As used herein, the terms "pharmaceutically acceptable", "physiologically tolerable" and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to or upon a human without the production of undesirable physiological effects such as nausea, dizziness, gastric upset and the like.

The preparation of a pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art. Typically such compositions are prepared as sterile injectables either as liquid solutions or suspensions, aqueous or non-aqueous, however, solid forms suitable for solution, or suspensions, in liquid prior to use can also be prepared. The preparation can also

be emulsified.

Suitable pharmaceutical carriers include sterile aqueous solution and various organic solvents and inert solid diluents or fillers. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like and combinations thereof.

In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like which enhance the effectiveness of the active ingredient. It is preferred that the formulation has a pH within the range of 3.5-8, such as in the range 4.5-7.5, such as in the range 5.5-7, such as in the range 6-7.5, most preferably around 7.3. However, as is understood by one skilled in the art, the pH range may be adjusted according to the individual treated and the administration procedure. For example, some GHS-R 1a secretagogues may be easily stabilised at a lower pH, so in another preferred embodiment of the the invention the formulation has a pH within the range 3.5-7, such as 4-6, such as 5-6, such as 5.3-5.7, such as 5.5.

Liquid compositions can also contain liquid phases in addition to and to the exclusion of water. Exemplary of such additional liquid phases are glycerin, vegetable oils such as cottonseed oil, organic esters such as ethyl oleate, and water-oil emulsions.

The pharmaceutical composition can include a pharmaceutically acceptable salt of the GHS-R 1a secretagogue therein. The salt will be one which is acceptable in its therapeutic use. By that it is meant that the salt will retain the biological activity of the GHS-R 1a secretagogue and the salt will not have untoward or deleterious effects in its application and use in treating diseases.

Pharmaceutically acceptable salts are prepared in a standard manner. If the GHS-R 1a secretagogue is a base it is treated with an excess of an organic or inorganic

acid in a suitable solvent. If the GHS-R 1a secretagogue is an acid, it is treated with an inorganic or organic base in a suitable solvent.

The pharmaceutically acceptable salt may be an acid addition salts including salts of inorganic acids as well as organic acids. Acid addition salts are formed with free amino groups of the GHS-R 1a secretagogue. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydriodic, metaphosphoric, phosphoric, sulpfuric and nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, ethylenediaminetetraacetic (EDTA), p-aminobenzoic, glutamic, benzenesulfonic and ptoluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutical acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference. The metal salt may be an alkali metal or earth alkali metal salt. Examples of metal salts include lithium, sodium, potassium and magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium and tetramethylammonium salts and the like.

Salts formed with the free carboxyl groups can be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine and the like.

Also included within the scope of pharmaceutical acceptable acid addition salts of a GHS-R 1a secretagogue is any hydrate (hydrated form) thereof.

The pharmaceutical composition for use in the invention may further comprise transport molecules. Transport molecules are primarily added in order to increase the half-life of the a GHS-R 1a secretagogue to be used in the invention comprising an anchor group, by preventing premature cleavage of the anchor group or part

thereof from the amino acid backbone of the secretagogue. Transport molecules act by having incorporated into or anchored to it the relevant GHS-R1A secretagogue.

Thus, in a preferred aspect of the invention the GHS-R1a secretagogue compound is administered with a substance capable of increasing the half-life of the secretagogue compound, for example by incorporating the GHS-R1a secretagogue compound into liposomes, micelles, iscoms, and/or microspheres or other transport molecules, in particular to protect the modified amino acid from being desacylated.

Any suitable transport molecules known to the skilled person may be used. Examples of transport molecules are those described in the conjugate section. Other preferred examples are liposomes, micelles, and/or microspheres.

Conventional liposomes are typically composed of phospholipids (neutral or negatively charged) and/or cholesterol. The liposomes are vesicular structures based on lipid bilayers surrounding aqueous compartments. They can vary in their physiochemical properties such as size, lipid composition, surface charge and number and fluidity of the phospholipids bilayers. The most frequently used lipids for liposome formation are: 1,2-Dilauroyl-*sn*-Glycero-3-Phosphocholine (DLPC), 1,2-Dimyristoyl-*sn*-Glycero-3-Phosphocholine (DMPC), 1,2-Dipalmitoyl-*sn*-Glycero-3-Phosphocholine (DPPC), 1,2-Distearoyl-*sn*-Glycero-3-Phosphocholine (DSPC), 1,2-Dioleoyl-*sn*-Glycero-3-Phosphocholine (DOPC), 1,2-Dimyristoyl-*sn*-Glycero-3-Phosphoethanolamine (DMPE), 1,2-Dipalmitoyl-*sn*-Glycero-3-Phosphoethanolamine (DPPE), 1,2-Dioleoyl-*sn*-Glycero-3-Phosphoethanolamine (DOPE), 1,2-Dimyristoyl-*sn*-Glycero-3-Phosphate (Monosodium Salt) (DMPA), 1,2-Dipalmitoyl-*sn*-Glycero-3-Phosphate (Monosodium Salt) (DPPA), 1,2-Dioleoyl-*sn*-Glycero-3-Phosphate (Monosodium Salt) (DOPA), 1,2-Dimyristoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] (Sodium Salt) (DMPG), 1,2-Dipalmitoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] (Sodium Salt) (DPPG), 1,2-Dioleoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] (Sodium Salt) (DOPG), 1,2-Dimyristoyl-*sn*-Glycero-3-[Phospho-L-Serine] (Sodium Salt) (DMPS), 1,2-Dipalmitoyl-*sn*-Glycero-3-[Phospho-L-Serine) (Sodium Salt) (DPPS), 1,2-Dioleoyl-*sn*-Glycero-3-[Phospho-L-Serine] (Sodium Salt) (DOPS), 1,2-Dioleoyl-*sn*-Glycero-3-Phosphoethanolamine-N-(glutaryl) (Sodium Salt) and 1,1',2,2'-Tetramyristoyl Cardiolipin (Ammonium Salt). Formulations composed of

DPPC in combination with other lipid or modifiers of liposomes are preferred e.g. in combination with cholesterol and/or phosphatidylcholine.

Long-circulating liposomes are characterized by their ability to extravasate at body sites where the permeability of the vascular wall is increased. The most popular way to produce long circulating liposomes is to attach hydrophilic polymer polyethylene glycol (PEG) covalently to the outer surface of the liposome. Some of the preferred lipids are: 1,2-Dipalmitoyl-*sn*-Glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)-2000] (Ammonium Salt), 1,2-Dipalmitoyl-*sn*-Glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)-5000] (Ammonium Salt), 1,2-Dioleoyl-3-Trimethylammonium-Propane (Chloride Salt) (DOTAP).

Possible lipid applicable for liposomes are supplied by Avanti, Polar lipids, Inc, Alabaster, AL. Additionally, the liposome suspension may include lipid-protective agents which protect lipids against free-radical and lipid-peroxidative damages on storage. Lipophilic free-radical quenchers, such as alpha-tocopherol and water-soluble iron-specific chelators, such as ferrioxianine, are preferred.

A variety of methods are available for preparing liposomes, as described in, e.g., Szoka et al., Ann. Rev. Biophys. Bioeng. 9:467 (1980), U.S. Pat. Nos. 4, 235,871, 4,501,728 and 4,837,028, all of which are incorporated herein by reference. Another method produces multilamellar vesicles of heterogeneous sizes. In this method, the vesicle-forming lipids are dissolved in a suitable organic solvent or solvent system and dried under vacuum or an inert gas to form a thin lipid film. If desired, the film may be redissolved in a suitable solvent, such as tertiary butanol, and then lyophilized to form a more homogeneous lipid mixture which is in a more easily hydrated powderlike form. This film is covered with an aqueous solution of the targeted drug and the targeting component and allowed to hydrate, typically over a 15-60 minute period with agitation. The size distribution of the resulting multilamellar vesicles can be shifted toward smaller sizes by hydrating the lipids under more vigorous agitation conditions or by adding solubilizing detergents such as deoxycholate. Additionally, the liposome suspension may include lipid-protective agents which protect lipids against free-radical and lipid-peroxidative damages on storage. Lipophilic free-radical quenchers, such as alpha-tocopherol and water-soluble iron-specific chelators, such as ferrioxianine, are preferred.

Micelles are formed by surfactants (molecules that contain a hydrophobic portion and one or more ionic or otherwise strongly hydrophilic groups) in aqueous solution. As the concentration of a solid surfactant increases, its monolayers adsorbed at the air/water or glass/water interfaces become so tightly packed that further occupancy requires excessive compression of the surfactant molecules already in the two monolayers. Further increments in the amount of dissolved surfactant beyond that concentration cause amounts equivalent to the new molecules to aggregate into micelles. This process begins at a characteristic concentration called "critical micelle concentration".

Common surfactants well known to one of skill in the art can be used in the micelles of the present invention. Suitable surfactants include sodium laureate, sodium oleate, sodium lauryl sulfate, octaoxyethylene glycol monododecyl ether, octoxynol 9 and PLURONIC F-127 (Wyandotte Chemicals Corp.). Preferred surfactants are nonionic polyoxyethylene and polyoxypropylene detergents compatible with IV injection such as, TWEEN-80, PLURONIC F-68, n-octyl-beta-D-glucopyranoside, and the like. In addition, phospholipids, such as those described for use in the production of liposomes, may also be used for micelle formation.

In a preferred embodiment of the invention the composition comprises a GHS-R 1a secretagogue or a salt thereof, as a lyophilisate and a solvent, said lyophilisate and said solvent being in separate compartments until administration. In another embodiment the composition is a solution of the GHS-R1A secretagogue or a salt thereof. In both embodiments the solvent may be any suitable solvent, such as described herein, and preferably the solvent is saline.

The invention also relates to a method for preparing a medicament or pharmaceutical composition comprising a compound for use in accordance with the invention, comprising admixing at least one GHS-R1A secretagogue or a salt thereof with a physiologically acceptable carrier.

The pharmaceutical composition comprising at least one GHS-R1A secretagogue, or a pharmaceutically acceptable salt thereof, may comprise one GHS-R1a secretagogue species, e.g. wildtype human ghrelin or a salt or hydrate thereof.

Alternatively, the pharmaceutical composition comprises at least two different GHS-R1A secretagogues or pharmaceutically acceptable salt(s) thereof, of which one e.g. is wildtype human ghrelin. The difference may for example be compounds having different anchor groups. For example, the pharmaceutical compositon may comprise both wild-type human ghrelin and L-692-429, produced by Merck.

In another embodiment, the pharmaceutical composition comprises at least one acylated GHS-R1A secretagogue, or a pharmaceutically acceptable salt thereof, in combination with a desacylated Ghrelin-like compound, or a pharmaceutically acceptable salt thereof, such as any of the desacylated ghrelin-like compounds described in WO03051389 (Theratechnologies: "Pharmaceutical compositions comprising unacylated ghrelin and therapeutical uses thereof"), incorporated herein by reference.

One suitable formulation for preparing pharmaceutical compositions for use in the present invention is described in Example 9 of PCT patent application PCT/DK2004/000519 (Gastrotech Pharma). An example of how one skilled in the art may investigate the pharmacokinetics of different formulations is given in Example 10 of PCT patent application PCT/DK2004/000519 (Gastrotech Pharma). Both Examples are incorporated herein by reference.

Compositions for parenteral administration

The GHS-R 1a secretagogue or a salt thereof may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. A pharmaceutical composition for parenteral administration may include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol, as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use.

The active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water. Aqueous solutions should be suitably

buffered if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Solutions of GHS-R1A secretagogues or pharmaceutically acceptable salts thereof can be prepared in water or saline, and optionally mixed with a nontoxic surfactant. Compositions for intravenous or intra-arterial administration may include sterile aqueous solutions that may also contain buffers, liposomes, diluents and other suitable additives.

Examples of oily or nonaqueous carriers, diluents, solvents or vehicles for parental use include propylene glycol, polyethylene glycol, animal, synthetic or vegetable oils, and injectable organic esters, and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Specific examples of oils useful in such compositions include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral compositions include oleic acid, stearic acid, and isostearic acid. Suitable organic esters include fatty acid esters such as ethyl oleate and isopropyl myristate.

Suitable soaps for use in parenteral compositions include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides; (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

The parenteral compositions typically will contain from about 0.5 to about 25% by weight of the active ingredient in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions

may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such compositions will typically range from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral compositions can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions comprising the active ingredient that are adapted for administration by encapsulation in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage.

Sterile injectable solutions are prepared by incorporating the compound(s) or pharmaceutically acceptable salt(s) thereof in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization.

Compositions for oral delivery

Those GHS-R1A secretagogue types capable of remaining biologically active in an individual after oral administration (such as short peptides) can be formulated in a wide range of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise the compounds of the invention or its pharmaceutically acceptable salt or a crystal form thereof as the active component. The pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders,

preservatives, wetting agents, tablet disintegrating agents, or an encapsulating material.

Preferably, the composition will be about 0.5% to 75% by weight of a compound or compounds of the invention, with the remainder consisting of suitable pharmaceutical excipients. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like.

In powders, the carrier is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain 1-70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the composition of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be as solid forms suitable for oral administration.

Drops can be used according to the present invention and may comprise sterile or non-sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100 °C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container aseptically. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride

(0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Other forms suitable for oral administration include toothpaste, gel dentrifrice orchewing gum. Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, emulsions, syrups and elixirs and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Compositions for topical administration

It is contemplated that the compounds of the invention can be delivered topically. Regions for topical administration include the skin surface. Compositions for topical administration via the skin and mucous membranes should not give rise to signs of irritation, such as swelling or redness.

The compounds described herein can be administered transdermally. Transdermal administration typically involves the delivery of a pharmaceutical agent for percutaneous passage of the drug into the systemic circulation of the patient. The skin sites include anatomic regions for transdermally administering the drug and include the forearm, abdomen, chest, back, buttock, mastoidal area, and the like.

The GHS-R1a secretagogues may be formulated for topical administration to the epidermis as ointments, creamse, gels or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents,

thickening agents, or coloring agents. Compositions suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions for aerosol, nasal or inhalation delivery

It is contemplated that the GHS-R1a secretagogues may be formulated for administration to the respiratory tract and including intranasal administration, and for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in a single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump. A suitable formulation for nasal administration is described in EP 1 466 610.

For inhalation, the compounds can be formulated as using methods known to those skilled in the art, for example an aerosol, dry powder or solubolized such as in microdroblets, preferably in a device intended for such delivery (such as commercially available from Aradigm, Alkerme or Nektar).

Compositions administered by aerosols may be prepared, for example, as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, employing fluorocarbons, and/or employing other solubilizing or dispersing agents in accordance with methods known in the art.

Administration as suppositories

It is contemplated that the GHS-R1a secretagogues to be used herein may also be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The active compound may be formulated into a suppository comprising, for example, about 0.5% to about 50% of a compound of the invention, disposed in a polyethylene glycol (PEG) carrier (e.g., PEG 1000 [96%] and PEG 4000 [4%].

Compositions for other types of delivery

Other types of delivery of the compounds in accordance with the present invention are also foreseen, such as implants.

Administration

Suitable dosing regimens for the various compounds and methods of the present invention are preferably determined taking into account factors well known in the art including type of subject being dosed; age, weight, sex and medical condition of the subject; the route of administration; the renal and hepatic function of the subject; the desired effect; and the particular compound employed.

Optimal precision in achieving concentrations of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

The present invention preferably deals with methods for administering a GHS-R1A secretagogue in a way which mimics the physiologically pre-meal situation as closely as possible yet providing patients in need of increased food intake, for example fragile elderly, post operative patients, patients with lost appetite as part of cachexia for example precipitated by cancer, cardiac disease etc. with a sufficient extra stimulatory input to their appetite regulating ghrelin receptors, which normally are reached by ghrelin in the pre-meal situation.

A typical dosage of a compound employed according to the invention (irrespective of administration route) is in a concentration equivalent to from 10 ng to 10 mg ghrelin per kg bodyweight. The dose level is based on the activity and the pharmacokinetic profile of the compound, i.e. the intrinsic *in vitro* activity relative to acylated ghrelin and the plasma curve observed in patients after administration of the compound. The selected dose is given to ensure that the resulting area under the activity curve

is equivalent to the area under the ghrelin activity curve. The concentrations and amounts herein are given in equivalents of amount ghrelin, wherein the ghrelin is the 28 aa human acylated ghrelin. The activity curve is defined as the plasma concentration curve multiplied by the intrinsic activity of the compound as measured using the methods described in the section entitled "Functionality", above.

In a preferred embodiment the medicament is administered in a concentration equivalent to from 0.1 μg to 1 mg ghrelin per kg bodyweight, such as from 0.5 μg to 0.5 mg ghrelin per kg bodyweight, such as from 1.0 μg to 0.1 mg ghrelin per kg bodyweight, such as from 1.0 μg to 50 μg ghrelin per kg bodyweight, such as from 1.0 μg to 10 μg ghrelin per kg bodyweight.

The administration route used must ensure that the non-degraded, bioactive form of the ligand will be the dominating form in the circulation, which will reach the GHS-R1a receptors and stimulate these. Thus, in order to obtain the maximum effect of the medicament it is preferably administered from one to three times daily, each administration being within 45 minutes of a meal, such as within 30 minutes of a meal, such as within 25 minutes of a meal, such as within 20 minutes of a meal, such as within 15 minutes of a meal, such as within 10 minutes of a meal, such as within 5 minutes of a meal. More preferred the medicament is administered prior to each main meal, such as administered three times daily. This administration scheme is applicable for all of the administrations route mentioned herein.

The compound may be administered in any suitable form, such as one or more of the following administration forms: oral, nasal, parenteral, including subcutaneously, intraveneously and intramuscularly, topical, buccal, sublingual, transdermal, inhalation, needle-free or in the form of a suppository.

Subcutaneous administration

Any parenteral administration form that will ensure that the ghrelin receptors which normally are the target for peripherally produced ghrelin in the premeal situation will be exposed to sufficient levels of the bioactive form of a GHS-R 1a secretagogue or a salt thereof to ensure robust and appropriate appetite stimulation, without causing desensitization of the system, may be part of the present invention. However, taken into consideration that the individuals to be treated possibly will have to receive

treatment for a longer period, such as weeks or months, it is preferred that the administration form is well suited herefor.

Accordingly, it is preferred that the GHS-R1A secretagogue or a salt thereof is administered subcutaneously in an amount sufficient to allow sufficient levels of the bioactive form, e.g. an acylated or anchorgroup containing form, to reach the receptors in time, such as prior to the forthcoming meal. Dose and frequency of administration by the subcutaneous route are as described above.

Bolus administration

Furthermore, from a molecular pharmacological point-of-view it is important to note that it has been found that the ghrelin receptor normally is exposed to short-lived surges in the concentrations of the natural agonist ligand, ghrelin. The GHS-R 1a receptor belongs to the class of receptors, so-called G protein coupled receptors or 7TM receptors, that upon continued exposure to an agonist will be desensitizised, internalized and down-regulated. These mechanisms, which are inherent to the overall signal transduction system, involve processes such as receptor phosphorylation (which in itself decreases the affinity of the receptor for the agonist) binding of inhibitory proteins such as arrestin (which sterically block the binding of signal transduction molecules such as G proteins). Another part of the agonist mediated desensitization process is receptor internalization (i.e. physical removal of the receptor from the cell surface where it could bind the agonist) as well as receptor down regulation (i.e. decreased production / expression of the receptor). Receptor internalization could after short-lived exposure of the receptor to agonist be followed by a re-sensitization process, where the receptor is dephosphorylated and recycled to the cell surface to be used again. Without being bound by theory, it is believed that, upon prolonged stimulation, which would occur for example during a long-lasting continuous infusion of the agonist, the receptor down-regulation process ensures that the target cell is adjusted in its signal transduction system etc. to this situation.

The present invention provides a procedure for an optimal administration of a GHS-R1A secretagogue to patients in order to obtain a maximal response and avoid for example desensitization mechanisms.

Accordingly, the present invention relates in one aspect to administration of a GHS-R1A secretagogue in boluses, preferably a bolus prior to each main meal. It has been found that a bolus administration leads not only to increase or maintenance of lean body mass but also stimulation of appetite, food intake and weight gain or maintainance of weight.

Without being bound by theory, it is believed that premeal subcutaneous injection, intravenous injection or short-term infusions of appropriate doses of a GHS-R1A secretagogue will ensure an increase or maintenance of lean body mass, and optionally a robust stimulation of appetite inducing GHS-1A receptors will be obtained with minimal constraint to the mobility etc. of the patient. Thus for example, patients with hip fractures can in the post operative situation be treated in the premeal period and if required during the meal as such, but will be free to move around and participate in the important post operative physicotherapeutic regimens.

Bolus administration is particularly relevant for increasing or maintaining lean body mass, weight, and/or appetite in an individual suffering from cachexia, such as cancer cachexia.

In one embodiment the medicament is administered by a suitable administration route as a bolus prior to a meal, said bolus comprising an amount of the GHS-R1A secretagogue or a salt thereof equivalent to from 0.3 μg to 600 mg ghrelin. More preferably, the medicament is administered as a bolus prior to a meal, said bolus comprising an amount of the GHS-R1A secretagogue or a salt thereof equivalent to from 2.0 μg to 200 mg ghrelin, such as from 5.0 μg to 100 mg ghrelin, such as from 10 μg to 50 mg ghrelin, such as from 10 μg to 5 mg ghrelin, such as from 10 μg to 1.0 mg ghrelin. In one preferred embodiment of the present invention, the GHS-R1A secretagogue according to the present invention is administered as a bolus in an amount equivalent to 10 μg per kg body weight or 2 x 10 μg per kg body weight. The exact dose depend, e.g. on the bioavailability of the composition in question, the higher the bioavailability the lower the dose.

Combination treatments

In a further aspect of the invention the present compounds may be administered in

combination with further pharmacologically active substances or therapeutic method or other pharmacologically active material, By the phrase "in combination" with another substance(s) and/or therapeutic method(s) is meant herein that said another substance(s) and/or therapeutic method(s) is administered to the individual thus treated before, during (including concurrently with) and/or after treatment of an individual with a secretagogue. In all cases of combination treatment described herein, the combination may be in the form of kit-in-part systems, wherein the combined active substances may be used for simultaneous, sequential or separate administration. In all cases, it is preferred that any of the herein-mentioned medicaments are administered in pharmaceutically effective amounts, i.e. an administration involving a total amount of each active component of the medicament or pharmaceutical composition or method that is sufficient to show a meaningful patient benefit.

Combination therapies for use in preferred embodiments of the present invention are grouped as follows:

1) Combinations wherein all active ingredients are appetite-regulating agents or in other ways useful for treating cachexia
2) Combinations of the secretagogue, such as ghrelin or a ghrelin-like compound, with an ingredient or therapy active against a disease causing or being associated with the disease or condition treated with the secretagogue, such as ghrelin or a ghrelin-like compound.
3) Combinations of the secretagogue, such as ghrelin or a ghrelin-like compound, with an ingredient or therapy active against symptoms associated with the disease or condition treated with the secretagogue, such as ghrelin or a ghrelin-like compound.

Such combinations are disclosed in PCT patent application PCT/DK2004/000519 (Gastrotech Pharma), incorporated herein by reference.

A further desirable combination for use in treating individuals in need thereof is a combination of the GHS-R1a secretagogue, such as ghrelin or a ghrelin-like compound, with an ingredient or therapy used to treat individuals suffering from cancer. Thus, in one embodiment, said GHS-R1a secretagogue is administered in

combination with cytotoxic chemotherapy and/ or radiation therapy and/or a surgical procedure.

The GHS-R1a secretagogue may also be administered in combination with an ingredient or therapy useful in a supportive care regimen, such as one or more of the following:

- G-CSF (and analogues thereof)
- EPO (and analogues thereof)
- Cannabinoid(s)
- Progestagen(s)
- Androgen(s) (such as SARM and androgen receptor modulators).
- Analgetics such as opioids

In one preferred embodiment of the present invention (preferably for treatment or prophylaxis of COPD), ghrelin is administered with one or more of the following:

- short acting inhaled beta-agonists such as albuterol
- inhaled combination product containing both anticholinergics (ipratropium) and beta-agonists (albuterol), such as Combivent
- anticholinergic agents
- bronchodilators
- inhaled anticholinergics such as ipratropium (Atrovent)
- inhaled corticosteroid
- oral corticosteroids in COPD
- inhaled glucocorticosteroids
- Theophylline
- oxygen
- mukolytic or mucus thinner, such as guaifenasin can be used
- High water intake

In another preferred embodiment, the secretagogue is administered to a lung transplant patient in combination with one or more immunosuppressive agents and/or one or more antimicrobial agents, optionally with one or more of the above-mentioned compounds.

Combinations wherein active ingredients are appetite-regulating agents

The secretagogue(s) according to the invention can also be administered in combination with other appetite-regulating agents, including more than one type of growth hormone secretagogue, such as another ghrelin-like compound, such as a ghrelin-like compound comprising a structure defined by formula I, described herein. Other secretagogues suitable for combination administration with another secretagogue compound are any of the secretagogue compounds described herein. In one preferred embodiment of the present invention, wild type ghrelin (most preferably human wild type ghrelin) is administered in combination with a different, ghrelin-like compound – this combination is envisaged to enhance and/or prolong the effect of the secretagogues on the ghrelin receptor. In another preferred embodiment of the present invention, a ghrelin-like compound that is not wild type ghrelin is administered in combination with a different ghrelin-like compound that is not wild-type ghrelin– again, this combination is envisaged to enhance and/or prolong the effect of the secretagogues on the ghrelin receptor. In a similar way, several different secretagogues may be administered to an individual to increase efficacy on the ghrelin receptor – such as greater than 2 different secretagogue types, such as 3, such as 4, such as 5, such as 6, such as 7, such as greater than 8 different secretagogue types. The secretagogue according to the invention, such as ghrelin or a ghrelin-like compound(s) can also be administered in combination with a pharmaceutically effective amount of a growth hormone, including hGH.

In one preferred embodiment of the present invention the secretagogue, such as ghrelin or a ghrelin-like compound, may be administered in combination with IGF-1, IGFBP-3, or ALS, preferably with IGF-1. The rationale behind this combination treatment is to increase the level of IGF-1, IGFBP-3, and/or ALS found to be low in cachectic individuals. In a further embodiment of the invention, the secretagogues, such as ghrelin or a ghrelin-like compound, may be administered in combination with compounds known to stimulate appetite, such as melanocortin receptor

antagonists, neuropeptide Y receptor agonists including agonists selective for individual subtypes of the neuropeptide Y receptors, leptin or leptin receptor agonists, cannabinoids including marijuana and marijuana derivatives, antipsychotics, especially atypical antipsychotics such as sertindole, Sulpirid, Clozapine, Risperidone, Quetiapin, Amisulpride, Ziprasidon, and Olanzapine.

Medical packaging

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art.

It is preferred that the compound(s) to be used according to the invention are provided in a kit. Such a kit typically contains an active compound in dosage forms for administration. A dosage form contains a sufficient amount of active compound such that a desirable effect can be obtained when administered to a subject, preferably prior to at least one meal a day, more preferably prior to each main meal, such as three times a day, during the course of 1 or more days.

Thus, it is preferred that the medical packaging comprises an amount of dosage units corresponding to the relevant dosage regimen. Accordingly, in one embodiment, the medical packaging comprises a pharmaceutical composition comprising a compound as defined above or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carriers, vehicles and/or excipients, said packaging having from 7 to 21 dosage units, or multipla thereof, thereby having dosage units for one week of administration or several weeks of administration.

In one embodiment the medical packaging is for administration once daily in a week, and comprises 7 dosage units, in another embodiment the medical packaging is for administration twice daily, and comprises 14 dosage units. In yet another more preferred embodiment the medical packaging is for administration three times daily, and comprises 21 dosage units.

The dosage units are as defined above, i.e. a dosage unit preferably comprises an amount of the GHS-R1a secretagogue or a salt thereof equivalent to from 0.3 μg to 600 mg ghrelin, such as of from 2.0 μg to 200 mg ghrelin, such as from 5.0 μg to 100 mg ghrelin, such as from 10 μg to 50 mg ghrelin, such as from 10 μg to 5 mg ghrelin, such as from 10 μg to 1.0 mg ghrelin.

The medical packaging may be in any suitable form for parenteral, in particular subcutaneous administration. In a preferred embodiment the packaging is in the form of a cartridge, such as a cartridge for an injection pen, the injection pen being such as an injection pen known from insulin treatment.

When the medical packaging comprises more than one dosage unit, it is preferred that the medical packaging is provided with a mechanism to adjust each administration to one dosage unit only.

Preferably, a kit contains instructions indicating the use of the dosage form to achieve a desirable affect and the amount of dosage form to be taken over a specified time period. Accordingly, in one embodiment the medical packaging comprises instructions for administering the pharmaceutical composition. In particular said instructions may include instructions referring to administration of said pharmaceutical composition either during a meal, or preferably at the most 45 minutes prior to a meal, such as at the most 30 minutes prior to a meal, such as at the most 25 minutes prior to a meal, such as at the most 20 minutes prior to a meal, such as at the most 15 minutes prior to a meal, such as at the most 10 minutes prior to a meal, such as at the most 5 minutes prior to a meal.

Examples

Example 1

Patients with advanced cancer suffering from the anorexia/cachexia syndrome (ACS), such as patients with any type of advances, incurable cancer, are believed to benefit from the present invention in terms of increased or maintained lean body mass, together with one or more of: improved quality of life, increased appetite, increased food intake, maintenance or gain of weight, food pleasantness, and/or fat deposition.

Patients are treated for 60 minutes with ghrelin dissolved in 250 ml normal saline (NaCl 0.9%) at a dose of 10 pmol/kg/minute (equals 0.0336 mcg/kg/min).

Investigational treatment: ghrelin is available in GMP-quality in prepared vials of 88 mcg from Calbiochem-Novabiochem AG, CLINALFA, Merck Biosciences, Switzerland. Placebo consists of an empty 250 ml normal saline infusion, which will be provided by a hospital pharmacy. Ghrelin is dissolved in saline and dose of 0.0336 mcg/kg/min ghrelin will be administered to the patient.

Assessments of efficacy:

- eating related symptoms: assessed using an adapted version of the "Functional Assessment of Appetite and Cachexia therapy (FAACT) questionnaire; the EORTC-QLQ-30 Anorexia/Cachexia questionnaire; the NCCTG – Anorexia/Cachexia questionnaire and the Edmonton Sympton assessment scale.
- Quality of life: will be assessed using the EORTC-QLQ-C30 questionnaire
- Nutritional intake and food preferences: food intake measurement will be by percentage calculation of food products consumed at each meal by the patient, the clinical dietician will assess the food preferences as part of their routine assessments.
- Food pleasantness: will be assessed after lunch using visual analogue scales, following established anchors
- Perceived appetite, hunger, nausea and satiety: will be assessed in the morning, before infusion, and before and after lunch using visual analogue scale, following established anchors. We will also apply a shortened ad hoc taste questionnaire.
- Growth hormone (GH): since GH reflects directly the biological function of ghrelin, with a rapid increase of GH after ghrelin injections, we will also monitor GH levels at the same time points as ghrelin. A standard ghrelin assay will be used.
- Body composition: body compositions will be assessed by BMI, bioimpedance analysis and dual photon absorptiometry/dual energy x-ray absorptiometry (DEXA). Albumin and transferrin levels will be determined as parameters for nutritional status.
- Cardiovascular autonomic function: for the screening of autonomic disorders a 20 minute holter ekg will be performed, and the SDNN value determined.

- Mediators of the primary anorexia/cachexia syndrome: mediators of the proinflammatory reaction (CRP, IL-6, TNF-alpha), the activated metabolism (free fatty acids, triglycerides, insulin, glucose, leptin), the gut-brain axis (ghrelin), and the somatotrophic axis (IGF-1, free testosterone) will be determined as baseline in the first week. A urine sample will be asserved for assessment of proteolysis-inducing factor (PIF), a mediator of the paraneoplastic anorexia/cachexia syndrome.

Example 2

Pre-clinical model:

Randomised, placebo-controlled trial evaluating long-term ghrelin therapy in rats undergoing allogeneic, single lung transplantation.

Design: All surgical procedures will be performed under general anaesthesia. Left donor lungs will be harvested from forty donor rats and flushed with a standard preservation solution. Recipient rats will undergo left thoracotomy and following pneumonectomy the pulmonary artery, main bronchus, and pulmonary vein of the donor lung will be anastomosed with the corresponding recipient structures. Postoperatively the transplanted rats will receive subcutaneous injections of ghrelin at a dose of 100 mg/kg or placebo twice daily for 8 weeks.

Endpoints: 24-h food intake and body weight will be measured at baseline and at weekly intervals throughout the study. Lean body mass will be assessed by DEXA scanning at baseline, 1 week and 8 weeks after transplantation.

Example 3

Clinical proof-of-concept study:

Randomised, placebo-controlled trial evaluating longterm ghrelin therapy in malnurished patients undergoing lung transplantation.

Design: Fifty patients with end-stage lung COPD and BMI < 19 who are awaiting single lung transplantation will receive subcutaneous ghrelin at a dose of 15 mg/kg or placebo injections twice daily while on the waiting list and for 8 weeks after transplantation.

Endpoints: Appetite, food intake, body weight, lean body mass as assessed by DEXA scanning and quality-of-life as assessed by SF-36 will be measured at

baseline, 1 week and 8 weeks after surgery. The incidence of postoperative complications as well as the pre-and postoperative morbidity and mortality will be registered.

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Claims

1. Use of a GHS-R1a secretagogue for the preparation of a medicament for increasing or maintaining lean body mass in an individual in need of such treatment.

2. The use according to claim 1, wherein the GHS-R1a secretagogue is ghrelin or a pharmaceutically acceptable salt thereof.

3. The use according to claims 1 or 2, wherein the GHS-R1a secretagogue is a ghrelin-like compound or a pharmaceutically acceptable salt thereof

wherein the ghrelin-like compound comprises a structure defined by formula I

$Z^1 - (X^1)_m - (X^2) - (X^3)_n - Z^2$, wherein

Z^1 is an optionally present protecting group

each X^1 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

X^2 is any amino acid selected from naturally occurring and synthetic amino acids, said amino acid being modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

each X^3 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

wherein one or more of X^1 and X^3 optionally may be modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

Z^2 is an optionally present protecting group,

m is an integer in the range of from 1-10

n is 0 or an integer in the range of from 1-35.

4. The use according to claim 3, wherein m is an integer in the range of from 1-9, such as of from 1-8, such as of from 1-7, such as of from 1-6, such as of from 1-5, such as of from 1-4, such as of from 1-3, such as of from 1-2, such as 2.

5. The use according to any of claims 3 or 4, wherein X^2 is selected from the group of modified Ser, modified Cys and modified Lys, such as wherein X^2 is modified Ser.

6. The use according to any of claims 3 to 5, wherein the ghrelin-like compound is selected from a compound of

formula II Z^1 – Gly- $(X^1)_{m-1}$ – (X^2) – $(X^3)_n$- Z^2,

formula III Z^1 – Gly- Ser – (X^2) – $(X^3)_n$- Z^2, and

formula IV Z^1 – Gly – (X^2) – $(X^3)_n$- Z^2.

7. The use according to any of claims 3 to 6, wherein $(X^3)_n$ comprises a sequence selected from one or more of the sequences shown below:

Phe Leu Ser Pro Glu His Gln

Phe Leu Ser Pro Glu His

Phe Leu Ser Pro Glu

Phe Leu Ser Pro

Phe Leu Ser

Phe Leu

Phe

8. The use according to any of claims 3 to 7, wherein n is an integer in the range of from 1-25, such as of from 1-24, such as from 1-15, such as of from 1-10, such as of from 10-25, such as of from 10-24, such as of from 15-25, such as of from 15-24.

9. The use according to any of claims 3 to 8, wherein $(X^3)_n$ is selected from one or more of the sequences shown below:

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln Pro Arg

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln Pro

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro Ala Lys Leu

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro Ala Lys

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro Ala

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser Lys

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu Ser

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys Glu

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg

Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln

Phe Leu Ser Pro Glu His Gln Arg Val Gln

Phe Leu Ser Pro Glu His Gln Arg Val

Phe Leu Ser Pro Glu His Gln Arg

Phe Leu Ser Pro Glu His Gln

Phe Leu Ser Pro Glu His

Phe Leu Ser Pro Glu

Phe Leu Ser Pro

Phe Leu Ser

Phe Leu

Phe

10. The use according to any of claims 3 to 9, wherein the acyl group is selected from a C1-C35 acyl group, such as a C1 – C20 acyl group, such as a C1 – C15 acyl group, such as a C6 – C15 acyl group, such as a C6 – C12 acyl group, such as a C8 – C12 acyl group.

11. The use according to any of claims 3 to 10, wherein the acyl group is selected from the group of C7 acyl group, C8 acyl group, C9 acyl group, C10 acyl group, C11 acyl group, and C12 acyl group.

12. The use according to any of claims 3 to 11, wherein the acyl group is selected from the group of C8 acyl group, and C10 acyl group.

13. The use according to any of claims 3 to 12, wherein the acyl group is selected from the group of C7 acyl group, C9 acyl group, and C11 acyl group, such as from the group of C9 acyl group and C11 acyl group.

14. The use according to any of the preceding claims, wherein the ghrelin-like compound is having formula III or having SEQ ID NO: 1.

15. The use according to any of the preceding claims, wherein the increase of lean body mass is an increase in overall percentage lean body mass, such as increasing an individual's percentage lean body mass by more than 0.5 %, such as more than 0.75%, such as more than 1%, for example more than 1.25%, such as more than 1.5%, for example more than 1.75%, such as more than 2%, for example more than 2.25%, such as more than 2.5%, for example more than 2.75%, such as more than 3%, for example more than 3.25%, such as more than 3.5%, for example more than 3.75%, such as more than 4%, for example more than 4.25%, such as more than 4.5%, for example more than 4.75%, such as more than 5%, for example more than 5.25%.

16. The use according to any of the preceding claims, wherein said increase or maintenance of lean body mass is in combination with:

a) prophylaxis or treatment of cachexia, and/or

b) stimulation of appetite.

17. The use according to any of the preceding claims, wherein the medicament formulation comprises the secretagogue or a pharmaceutically acceptable salt thereof.

18. The use according to any of the preceding claims, wherein the medicament is in a formulation for parenteral, intravenous, intramuscular or subcutaneous administration.

19. The use according to any of claims 17 to 18, wherein the formulation comprises the secretagogue or a salt thereof as a lyophilisate and the formulation further comprises a solvent, said lyophilisate and said solvent being in separate compartments until administration.

20. The use according to any of claims 17 to 19, wherein the formulation is a solution of the secretagogue or a salt thereof.

21. The use according to claim 19 to 20, wherein the solvent is saline.

22. The use according to any of the preceding claims, wherein the medicament is administered prior to or during a meal.

23. The use according to any of the preceding claims, wherein the medicament is administered in a concentration equivalent to from 10 ng to 10 mg ghrelin per kg bodyweight.

24. The use according to any of the preceding claims, wherein the medicament is administered from one to three times daily, preferably once prior to or during breakfast and/or once prior to or during lunch and/or once prior to or during dinner.

25. The use according to any of the preceding claims, wherein the individual has a lean body mass of less than 80% of normal, such as less than 60% of normal and/or a body mass index below 17 kg/m^2.

26. The use according to any of the preceding claims, wherein the medicament is given until the lean body mass is more than 60% of normal, preferably more than 80% of normal, more preferably more than 90% of normal.

27. The use according to any of the preceding claims, wherein the medicament is administered in a concentration equivalent to from 0.1 μg to 1 mg ghrelin per kg

bodyweight, such as from 0.5 μg to 0.5 mg ghrelin per kg bodyweight, such as from 1.0 μg to 0.1 mg ghrelin per kg bodyweight, such as from 1.0 μg to 50 μg ghrelin per kg bodyweight, such as from 1.0 μg to 10 μg ghrelin per kg bodyweight.

28. The use according to any of the preceding claims, wherein the medicament is administered as a bolus prior to or during a meal, said bolus comprising an amount of the GHS-R1a secretagogue or a salt thereof equivalent to from 0.3 μg to 600 mg ghrelin

29. The use according to any of the preceding claims, wherein the medicament is administered as a bolus prior to or during a meal, said bolus comprising an amount of the GHS-R1a secretagogue or a salt thereof equivalent to from 2.0 μg to 200 mg ghrelin, such as from 5.0 μg to 100 mg ghrelin, such as from 10 μg to 50 mg ghrelin, such as from 10 μg to 5 mg ghrelin, such as from 10 μg to 1.0 mg ghrelin.

30. The use according to any of the preceding claims, wherein the medicament is administered from one to three times daily, each administration being during a meal or at the most 180 minutes prior to a meal, such as at the most 90 minutes prior to a meal, e.g. at the most 45 minutes prior to a meal, such as at the most 30 minutes prior to a meal, such as at the most 25 minutes prior to a meal, such as at the most 20 minutes prior to a meal, such as at the most 15 minutes prior to a meal, such as at the most 10 minutes prior to a meal, such as at the most 5 minutes prior to a meal.

31. The use according to any of the preceding claims, wherein the medicament is administered three times daily.

32. The use according to any of the preceding claims, wherein the cancer cachexia is caused by a catabolic disorder.

33. The use according to any of the preceding claims, wherein the cancer cachexia is caused by an anorectic disorder.

34. The use according to any of the preceding claims, where the individual is suffering from a cancer selected from lung cancer, pancreatic cancer, liver cancer, and GI tract cancers.

35. Use according to any of the preceding claims, wherein said medicament is administered in combination with a chemotherapy medicament.

36. Use of a secretagogue compound for the preparation of a medicament for the treatment of an individual suffering from, or at risk of suffering from, chronic obstructive pulmonary disease.

37. The use according to claim 36, wherein the secretagogue is according to any of claims 2-14.

38. The use according to any of the preceding claims, wherein the individual is a lung transplant patient.

39. The use according to claim 38, wherein the medicament is given during the pre-operative period.

40. The use according to claim 38, wherein the medicament is given during the peri-operative period.

41. The use according to claim 38, wherein the medicament is given during the post-operative period.

42. The use according to claims 38, wherein the medicament is given during the pre-operative, the peri-operative and the post-operative period.

43. The use according to any of claims 36-42 wherein the medicament is administered according to any of claims 22-31.

44. The use according to any of claims 36-43, wherein the medicament is formulated according to any of claims 17-21.