PHARMACEUTICAL FORMULATIONS FOR MAINTAINING LEAN MUSCLE MASS DURING WEIGHT LOSS TREATMENT

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations and methods useful for maintaining lean muscle mass during treatment with a glucagon-like peptide 1 (GLP-1) receptor agonist or a dual GLP-1/ glucose-dependent insulinotropic polypeptide (GIP) agonist.

All publications, patents, patent applications, and other references cited in this application are incorporated herein by reference in their entirety for all purposes and to the same extent as if each individual publication, patent, patent application or other reference was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Citation of a reference herein shall not be construed as an admission that such is prior art to the present invention.

BACKGROUND OF THE INVENTION

GLP-1 and dual GLP-1/GIP agonists have grown in popularity as a weight loss drug among those with or without obesity. The loss of fat mass in obese subjects has health benefits, but concomitant loss of muscle and bone, particularly in older subjects, has the potential to adversely affect health and lifespan. Although with loss of weight an amount of lean mass loss is inevitable, ideally safe and effective treatment of obesity should minimize reductions in lean mass with the objective of improving body composition by increasing the proportion of lean to fat mass.

A need exists in the art for pharmaceutical formulations and methods for maintaining lean muscle mass during weight loss treatment.

SUMMARY OF THE INVENTION

In one aspect of the invention, provided is a method for maintaining lean muscle mass during weight loss treatment, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) and a therapeutically

effective amount of a glucagon-like peptide (GLP-1) receptor agonist, or a pharmaceutically acceptable salt individually thereof.

In another aspect of the invention, provided is a pharmaceutical formulation, comprising:

- therapeutically effective amount of a GHS, or a pharmaceutically acceptable salt thereof;
- a therapeutically effective amount of a GLP-1 receptor agonist or a dual GLP-1/GIP agonist, or a pharmaceutically acceptable salt individually thereof; and
- a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows body weight of DIO mice at day 14 of treatment.

Figure 2 shows percentage lean mass, percentage fat mass, and lean:fat mass ratio of DIO mice at day 14 of treatment.

DETAILED DESCRIPTION OF THE INVENTION

The inventors discovered that growth hormone secretagogues (e.g. ibutamoren, also referred to herein as LUM-201 or MK-0677) in combination with a glucagon-like peptide receptor agonist can maintain lean muscle mass during weight loss treatment. Several clinical trials have tested semaglutide and other GLP-1 receptor (GLP-1R) agonists for treating obesity, but in many published studies of GLP-1 agonists body composition was not included as a primary endpoint. According to U.S. FDA guidelines the primary efficacy endpoint for a weight loss drug is related to changes in body weight. Metrics of body composition are considered safety endpoints which require testing smaller cohorts which potentially underpowers the significance of the studies. Accordingly, just a fraction of subjects in phase III trials receive measurements of body composition, therefore conclusions about the effects of GLP-1R agonists on body composition are limited.

Treatment of subjects with a GLP1 receptor agonist (GLP-1R) or with a combined glucose - dependent insulinotropic polypeptide (GIP) receptor dual receptor agonist results in significant loss of fat mass accompanied by loss of lean mass. By contrast, when these treatments are combined with ibutamoren administration the accompanying loss in lean mass is significantly reduced.

It has been proposed that the GLP-1R agonist semaglutide lowers body weight by direct interaction with diverse GLP-1R populations and by affecting the activity of neural pathways involved in food intake, reward, and energy expenditure (Gabery et al.2020). In contrast to GLP1 administration of the hormone ghrelin stimulates food intake and is involved in increasing fat deposition (Wiedmer et al., 2007). Several lines of evidence suggest a role for both ghrelin and GLP-1 signaling in the regulation of food intake (Decarie-Spain and Konoski 2021). Indeed, the data supports the notion that ghrelin and GLP-1 are mutual antagonists acting through distinct receptors.

Surprisingly, the GHSR agonists ghrelin and ibutamoren exhibit different biological properties. Ghrelin is an agonist for the growth hormone secretagogue receptor (GHSR) and ghrelin administration is generally associated with increasing food intake and fat deposition. ibutamoren is a synthetic GHSR agonist. Yet, surprisingly, when humans were treated for up to 12 mo with ibutamoren they exhibited no increase in fat mass, but lean mass increased, without an overall increase in appetite (Nass et al. 2008). This surprising finding of beneficial effects on body composition with ibutamoren was confirmed in obese subjects treated with ibutamoren for 2 mo (Svensson et al. 1998). Fat mass did not increase, but an increase in lean body mass was observed. In another study treatment with ibutamoren was shown to reverse diet-induced catabolism in humans (Murphy, 1998). Since ibutamoren and ghrelin both bind and activate GHSR the findings were surprising.

The fact that ibutamoren did not increase fat mass, but increased lean mass, is the opposite to what would have been predicted based on the known effects of ghrelin. In the field the general consensus, based on results from animal studies, is that ghrelin increases food intake and fat deposition (Wiedmer et al., 2007; Decarie-Spain and Kanoski, 2021). Ghrelin and ibutamoren are markedly different in structure, Ghrelin is an octanoylated 28-aminoacid peptide, whereas

ibutamoren is a spiropiperidine (Patchett et al. 1995). Although ghrelin and ibutamoren bind to and activate GHSR, GHSR site-directed mutagenesis studies show that ibutamoren and ghrelin bind to different sites on GHSR (Sun et al 2022). This difference, in concert with distinct structural differences of the molecules likely explains their different biological actions. In addition, while both ghrelin and ibutamoren stimulate GH release, ibutamoren administration produces a sustained increase in the amplitude of pulsatile GH release and a sustained increase in circulating IGF-1; neither is observed following ghrelin administration. The increase in IGF-1 induced by ibutamoren also explains ibutamoren-mediated increases in lean mass. It is also relevant that the negative regulator of muscle growth, myostatin, reduces IGF-1 production and signaling.

Before the discovery by the inventors of the biological impact of ibutamoren on increasing IGF-1 levels and increasing lean mass, the prediction by experts would be that combination treatment with a GHSR agonist, like ghrelin, would antagonize the suppressive effects of GLP1-R agonists on food intake and fat reduction. Therefore, the findings of the inventors support the novelty of claimed invention to administer ibutamoren to limit loss of lean mass under conditions of weight reduction induced by either fasting, or fat loss induced by any appetite suppressing agent.

In the first trial (STEP 1) showing efficacy of the GLP-1 receptor agonist semaglutide in treating adult obesity a subset of 140 patients underwent body composition analysis. In these patients lean mass accounted for approximately 39% of total weight loss. Such a loss in lean mass associated with dramatic weight reduction is acceptable provided overall body composition improves; however, not all obese patients can afford to lose significant lean mass. Sarcopenic obesity that is common in the elderly is associated with a combination of the risks of having excess fat and low levels of skeletal muscle. Any additional lowering of lean mass among those with sarcopenia likely imposes a greater threat to health and longevity than the presence of excess fat. Hence, there is a need to minimize loss of lean mass in these patients.

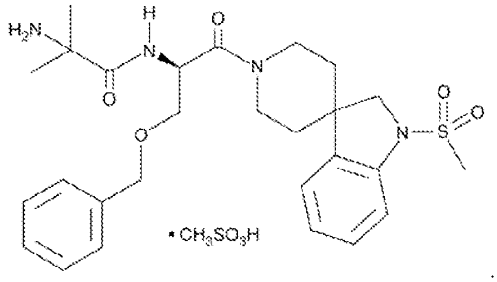
The inventors developed a pharmaceutical formulation to maintain lean mass in patients treated with GLP-1R agonists for obesity by including a formulation comprising the GH-secretagogue ibutamoren (aka MK-0677). This compound has been shown to reverse diet-induced nitrogen

wasting in humans, suggesting that patients who are catabolic because of reduced caloric intake would benefit from oral treatment with ibutamoren (Murphy et al., 1998).

In addition, the treatment of healthy obese males with ibutamoren produces a sustained increase in serum levels of GH, IGF-I, and IGF-binding protein-3. This resulted in anabolic changes in body composition and energy expenditure with a sustained increase in fat-free mass and a transient increase in basal metabolic rate (Svensson et al., 1998).

Myostatin production has a negative impact on muscle mass. Inhibition of myostatin signaling with a monoclonal antibody is reported to have beneficial effects on skeletal muscle in GLP-1 treated non-human primates (Mastaitis et al. 2023). However, an alternative to antagonism of myostatin action is to suppress the endogenous production of myostatin. Growth hormone (GH) reduces myostatin levels (Liu et al., 2003). The inhibitory effect of GH on myostatin production is sustained during 12 and 18 months of GH treatment. This lowering of myostatin by GH was associated with increases in lean body mass and translated into enhanced aerobic performance as determined by maximal oxygen uptake and ventilation threshold. Given the potent catabolic actions of myostatin and its suppression by GH these data suggest that myostatin represents a potential key target for GH-induced anabolism (Liu et al., 2003). Endogenous pulsatile GH release declines during aging and is associated with loss of muscle and declining strength. However, once daily oral GH-secretagogue ibutamoren increases the amplitude of pulsatile GH release to levels observed in young adults; therefore, rather than treatment with a myostatin antagonist, which may elicit adverse effects, a more physiological approach is to reduce myostatin production by treating patients with ibutamoren that has been shown to be well tolerated in humans.

The structure of ibutamoren, also referred to herein as ibutamoren mesylate, is shown below:



Ibutamoren is commercially available from vendors such as, for example, Sigma Aldrich and Caymen Chemical.

In one aspect, 10-50 mg of ibutamoren is administered, for example, once daily. In one embodiment, 25-50 mg of ibutamoren is administered once daily. Other examples of the amount of ibutamoren administered include 10, 15, 20, 25, 30, 35, 40, 45, and 50 mg. In another aspect, ibutamoren is administered orally.

In one embodiment, 0.1-3.2 mg/kg of ibutamoren is administered. In another embodiment, 0.1-1.6 mg/kg of ibutamoren is administered. Other examples of the amount of ibutamoren administered include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1 and 3.2 mg/kg.

In another aspect, the GLP-1 receptor agonist is selected from:

exenatide (tradenames Byetta® and Bydureon®, typically dosed at 2 mg once/week by injection);

liraglutide (tradenames Victoza® and Saxenda®, typically dosed at 1.2 mg/day by injection);

lixisenatide (tradename Adylxin®, typically dosed at 20 μg/day by injection);

albiglutide (tradename Tanzeum®, typically dosed at 30 mg, once/week by injection);

dulaglutide (tradename Trulicity®, typically dosed at 0.75-1.5 mg once/week by injection); and,

semaglutide (tradename Ozempic®, typically dosed at 0.5-1.0 mg once/week by injection).

Other examples of the amount of dulaglutide administered include 0.8, 0.85, 0.9, 0.95, 1.0, 1.05, 1.1, 1.15, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45 and 1.5 mg once/week by injection.

Other examples of the amount of semaglutide include 0.5, 0.6, 0.7, 0.8, 0.9, 1.0 mg once/week by injection.

In another aspect, the GLP-1 or dual GLP-1/GIP receptor agonist can be selected from the following:

Names	**Dosage (mg)**	**Company**
Semaglutide - low dose	3 to 14	Novo
Semaglutide - high dose	25 and 50	Novo
Orforglipron	12, 24, 36, 45	Eli Lily

Danuglipron	40 to 200	Pfizer
GSBR-1290	30, 60, 90	Structure Therapeutics
RGT-075	15 to 180	Qilu Regor Pharma
TTP-273	150 (two tablets of 75mg)	vTv Therapeutics
ECC-5004	10 to 30	AZ
semaglutide + dapagliflozin	NA	Novo
amycretin	1 to 100	Novo
HSK-34890	5 to 80	Tibet Haisco Pharmaceutical Co Ltd

VCT-220	10 to 160	Suzhou Wingtech Pharma
TERN-601	30	Tern Pharma
PF-06954522	-	Pfizer
Tirzepatide	5, 10, 15	Eli Lilly
Retatrutide	-	Eli Lilly
maridebart cafraglutide	21 to 840	Amgen
LY-3493269	-	Eli Lilly
NN-9541	-	Novo
VK2735	-	Viking Therapeutics
VK2735	2.5 to 15	Viking Therapeutics
SCO-094	-	Scohia Pharma
CT-388	5 to 12	Carmot Therapeutics

The compounds of the invention can be administered or delivered simultaneously or sequentially. The timing of the dosage of the GHS and the GLP-1 or dual GLP-1/GIP agonist depends on their independent dosage regimen. Examples of dosage timing include:

(i.) Simultaneous dosing, single formulation. This can be achieved by co-formulating the drugs (two or three) into a single formulation (e.g., an oral dosage) and then administering the single formulation.

(ii.) Simultaneous dosing, different formulations. This can be achieved by independently administering the drugs at approximately the same time (e.g., different oral dosages, oral/injected dosages, or injected dosages).

(iii.) Simultaneous dosing + additional dosing. For drugs that are administered with overlapping timing (e.g., in the morning, but only one in the evening), one of regimens (i.) or (ii.) can be used followed by additional dosing of drugs.

(iv.) Non-simultaneous dosing. For drugs that are administered with different timing (e.g., daily oral dosage versus weekly injection), the drugs can be administered in accordance with their individual protocols.

In another aspect, the present invention provides a novel packaging kit, comprising:

(v.) at least one first compartment, comprising: a therapeutically effective amount of a growth hormone secretagogue (GHS) and a pharmaceutically acceptable carrier;

(vi.) at least one second compartment, comprising a therapeutically effective amount of a GLP-1 receptor agonist, and metformin and a pharmaceutically acceptable carrier.

Most of the approved drugs recited herein have a specific pharmaceutical salt (e.g., ibutamoren is a mesylate, ibutamoren mesylate). While the approved salt is what is referenced above, other pharmaceutically acceptable salts are considered to be part of the presently claimed invention.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also to be understood that each individual element of the embodiments is intended to be taken individually as its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

Definitions

"Treating" or "treatment" covers the treatment of a disease-state in a mammal, and includes: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, e.g., arresting it development; and/or (c) relieving the disease-state, e.g., causing regression of the disease state until a desired endpoint is reached. Treating also includes the

amelioration of a symptom of a disease, wherein such amelioration may or may not be directly affecting the disease (e.g., cause, transmission, expression, etc.).

"Pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 1, 2-ethanedisulfonic, 2-acetoxybenzoic, 2-hydroxyethanesulfonic, acetic, ascorbic, benzenesulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methanesulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluenesulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are useful. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, 1990, p 1445, the disclosure of which is hereby incorporated by reference.

"Therapeutically effective amount" includes an amount of a compound of the present invention that is effective when administered alone or in combination for the indicated treatment.

"Therapeutically effective amount" also includes an amount of the combination of compounds claimed that is effective to treat the desired indication.

The combination of compounds can be a synergistic combination. Synergy, as described, for example, by Chou and Talalay, Adv. Enzyme Regul. 1984, 22:27-55, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal or lower doses of the compounds. Synergy can be in terms of lower cytotoxicity, increased effect, or some other beneficial effect of the combination compared with the individual components.

In the present invention, the individual compounds of the present invention can be administered in any convenient manner (e.g., enterally or parenterally). Examples of methods of administration include orally and transdermally. One skilled in this art is aware that the routes of administering the compounds of the present invention may vary significantly. In addition to other oral administrations, sustained and/or modified release compositions may be favored. Other acceptable routes may include injections (e.g., intravenous, intramuscular, subcutaneous, and intraperitoneal); subdermal implants; and, buccal, sublingual, topical, rectal, vaginal, and intranasal administrations. Bioerodible, non-bioerodible, biodegradable, and non-biodegradable systems of administration may also be used. Examples of oral formulations include tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, powders, granules, and suspensions.

If a solid composition in the form of tablets is prepared, the active ingredient(s) can be mixed with a pharmaceutical vehicle, examples of which include silica, starch, lactose, magnesium stearate, and talc. The tablets can be optionally coated with sucrose or another appropriate substance or they can be treated so as to have a sustained or delayed activity and so as to release a predetermined amount of active ingredient continuously. Capsules can be obtained, for example, by mixing the active ingredient(s) with a diluent and incorporating the resulting mixture into soft or two piece hard capsules. By way of example, a syrup or elixir can contain the active ingredient(s) in conjunction with a sweetener, which is typically calorie-free, an

antiseptic (e.g., methylparaben and/or propylparaben), a flavoring, and an appropriate color. Water-dispersible powders or granules, for instance, can contain the active ingredient(s) mixed with dispersants or wetting agents or with suspending agents such as polyvinylpyrrolidone, as well as with sweeteners or taste correctors. Rectal administration can be effected using suppositories, which are prepared with binders melting at the rectal temperature (e.g., cocoa butter and/or polyethylene glycols), gels or foams. Parenteral administration can be effected using aqueous suspensions, isotonic saline solutions, or injectable sterile solutions, which contain pharmacologically compatible dispersants and/or wetting agents (e.g., propylene glycol and/or polyethylene glycol). The active ingredient(s) can also be formulated as microcapsules or microspheres, optionally with one or more carriers or additives. The active ingredient(s) can also be presented in the form of a complex with a cyclodextrin, for example α-, β-, or γ-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, and/or methyl-β-cyclodextrin.

The dose of the individual compounds of the present invention administered daily will vary on an individual basis and to some extent may be determined by the severity of the disease being treated. The dose of the compound of the present invention will also vary depending on the drug or drugs administered. Examples of dosages of compounds of the present invention have been provided above but may vary based on synergistic effects of a combination of two or three drugs.

The individual compounds can be administered in a single dose or in a number of smaller doses over a period of time. The length of time during which the compound is administered varies on an individual basis and can continue until the desired results are achieved.

The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

EXAMPLES

Example 1

Mice Studies

Male, diet-induced obese mice on a C57Bl/6J background (Jackson Laboratory #380050, 12 weeks) are single-housed and maintained on high fat diet (60 % kcal from fat, Research Diets D12492). Eight mice/group are treated with placebo, ibutamoren (0.4 – 4 mg/kg) or 0.12 mg/kg semaglutide ± 0.4 – 4 mg/kg ibutamoren daily for 28 days. Cumulative food intake is determined by manually weighing food from single cages daily. Mouse body weight is monitored daily. At 28 days blood glucose and insulin are measured showing reduced levels of glucose and insulin with semaglutide and semaglutide + ibutamoren treatment compared to vehicle. At 0, 7, 21 and 28 days body composition is assessed using an EchoMRI body composition analyzer. At 28 days mice are euthanized and muscles collected and weighed: tibalis anterior, soleus, extensor longus and gastrocnemius; muscle fiber cross sectional area is determined by H&E staining.

These measurements show that the combination of ibutamoren + semaglutide provides retention of muscle mass during weight loss compared to treatment with semaglutide alone. In another similarly treated cohort of mice an exercise performance protocol is used to measure VO_2 max and time to exhaustion. Mice treated with ibutamoren have greater VO_2 max values than control mice. Animals treated with semaglutide show a modest improvement in exercise capacity. VO_2 max values of animals in the ibutamoren + semaglutide group are greater than control. The time to exhaustion of animals in the three treatment groups trended to be greater than those of control animals with the largest effect in animals co-treated with ibutamoren and semaglutide.

Example 2

Dog Studies

Twenty-four male beagle dogs weighing 10-12 kg receive two cups of 5A4J HFHF canine diet daily (20.5% protein, 52.9% fat, 26.6% carbohydrate, 18.9% fructose plus water ad libitum. After 12 weeks dogs enter the drug combination study and receive either placebo, ibutamoren, or

semaglutide ± ibutamoren (N=6/group), once daily for 14- days. The dogs receive two cups of HFHF canine diet per day, with feeding 3 h post dose during the 14-day study.
Dogs are divided into 4 groups: injected subcutaneously (sc) with vehicle, semaglutide (0.25 – 2.4 mg/week), oral ibutamoren (0.4 – 1 mg/kg/day), semaglutide (sc 0-25 – 2.4 mg/week) + ibutamoren (0.4 – 1 mg/kg/day) for 2 -16 weeks. Food intake and body weight are measured daily.

At 2 weeks a post dose oral glucose tolerance test is performed in fasted dogs and reveals significant improvements in glucose excursions in treated dogs compared with placebo control. At 2 and 16 weeks, dogs receiving semaglutide show greater body weight loss than those receiving placebo. This correlates with significantly decreased cumulative food intake ($P < 0.05$). At 2, 8 and 16 weeks body composition is measured by Dexa. Compared to placebo treatment, semaglutide alone illustrates reductions in cumulative food intake and reduced fat and lean mass. The combination of semaglutide with ibutamoren reduces fat mass and inhibits the loss of lean mass.

Example 3

Interim Pre-clinical Studies on DIO Mice

This example evaluated the *in vivo* efficacy of the treatment with LUM-201 small molecule alone or in combination with semaglutide on metabolic parameters in the diet-induced obesity (DIO) model in mice. The test article "LUM-201" used in this study was provided by the Sponsor. The positive control (Semaglutide) is purchased by CBL. The vehicle (propylene glycol) is provided by CBL.

Male DIO model mice (C57BL/6, bodyweight > 40g) were employed to initiate this study. All animals were fed 60% HFD diet for > 18 weeks. After a one-week acclimation period, the following measurements (Echo MRI (fat and lean mass), OGTT, 4h FBG, and 4h FPI) were conducted in all mice to obtain the baseline data before grouping. Then all male DIO model mice were randomly assigned to groups based on body weight and fat mass on Day 0. Different groups were administered with different treatments as follows:

- Group 1 (Vehicle, N/A, Alzet pump, continuous from Day 0 to Day 28, N=10)

- Group 2 (LUM-201, 25 mg/kg/day, Alzet pump, continuous from Day 0 to Day 28, N=10)
- Group 3 (Treatment 1: Semaglutide, 10 nmol/kg/dose, s.c., QD from Day 0 to Day 28; Treatment 2: Vehicle, N/A, Alzet pump, continuous from Day 0 to Day 28, N=10)
- Group 4 (Treatment 1: Semaglutide, 10 nmol/kg/dose, s.c., QD from Day 0 to Day 28; Treatment 2: LUM-201, 25 mg/kg/day, Alzet pump, continuous from Day 0 to Day 28, N=10)

Clinical observations were performed daily, and any unusual signs or behaviors were recorded. Bodyweight measurements were performed before grouping and daily after grouping/day. Food intake evaluation were conducted daily per cage. All mice are to be euthanized on Day 29.

Readouts relevant to assessing the combination therapy (semaglutide and LUM-201) include:

1. Body weight.
2. EchoMRI will be performed on Day -3, Day 14, Day 21, and Day 27 for body composition.

Interim data summary

As described above, evaluation of the efficacy of single-agent and combination treatments were conducted for days 14, 21, and 27. Data for day 14, 21, and 27 time points are provided below. The set of data reviewed to assess the efficacy of the treatment regimens include: Body weight, percentage lean mass, percentage fat mass, and lean:fat mass ratio. Summary graphs of these data at Day 14 are included for review; similar data are observed at day 21 and 27. Significant findings are noted in the interim results statement below and in Figures 1 and 2.

Summary of day 14 and 21 results

- **Specific to assessing combination therapy** at the day 14 assessment, comparison of stand-alone therapy (semaglutide) with combination therapy (semaglutide + LUM-201) revealed significant changes in the following body composition measures:
    - lean body mass (relative increase in combination; all $p = 0.013$)
    - fat mass (relative decrease in combination; all $p = 0.019$)
    - lean:fat mass ratio (relative increase in combination; all $p = 0.017$)

- At day 14, significant weight loss (all $p \leq 0.0151$) was observed in all groups (LUM-201 alone, semaglutide alone, combination) compared to control.
- At day 14, significant changes were observed in all groups (LUM-201 alone, semaglutide alone, combination) for the body composition parameters:
    - lean body mass (increase relative to control; all $p \leq 0.010$)
    - fat mass (decrease relative to control; all $p \leq 0.0079$)
- At day 21 and 27, significant weight loss was maintained in all groups (LUM-201 alone, semaglutide alone, combination) compared to the vehicle control (all $p < 0.001$).
- At day 21 and day 27, significant changes in body composition parameters were maintained for all groups (LUM-201 alone, semaglutide alone, combination) relative to the vehicle control group:
    - lean body mass (increase relative to control; all $p \leq 0.002$)
    - fat mass (decrease relative to control; all $p \leq 0.0001$)
- **Specific to assessing combination therapy** at the day 21 assessment, comparison of stand-alone therapy (semaglutide) with combination therapy (semaglutide + LUM-201) revealed significant changes in the following body composition measures:
    - lean body mass (relative increase in combination; all $p = 0.015$)
    - fat mass (relative decrease in combination; all $p = 0.006$)
    - lean:fat mass ratio (relative increase in combination; all $p = 0.007$)
- **Specific to assessing combination therapy** at the day 27 assessment, comparison of stand-alone therapy (semaglutide) with combination therapy (semaglutide + LUM-201) revealed significant changes in the following body composition measures:
    - lean body mass (relative increase in combination; all $p = 0.020$)
    - fat mass (relative decrease in combination; all $p = 0.003$)
    - lean:fat mass ratio (relative increase in combination; all $p = 0.002$)

CONCLUSION of efficacy based on Day 14, Day 21, and Day 27 data

LUM-201, used in combination with semaglutide, augments the efficacy of semaglutide alone in the treatment of mice with diet-induced obesity. The combination therapy (LUM-201 dosed with semaglutide) improves weight loss compared with semaglutide alone. Importantly, the combination also appears to improve the preservation of lean muscle mass in the context of

weight loss compared with semaglutide treatment alone. Although the combination of ibutamoren and semaglutide were studied in this Example, it is contemplated that the results and conclusions would be similar to combinations of LUM-201 and other (GLP-1) receptor agonists or dual GLP-1/ glucose-dependent insulinotropic polypeptide (GIP) agonists of the invention. It is also contemplated that the combination of other GHS compounds and (GLP-1) receptor agonists or dual GLP-1/ glucose-dependent insulinotropic polypeptide (GIP) agonists of the invention would lead to similar results.

The invention is further described in the following numbered paragraphs:

1. A method for maintaining lean muscle mass during weight loss treatment, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) and a therapeutically effective amount of a glucagon-like peptide (GLP-1) receptor agonist, or a pharmaceutically acceptable salt individually thereof.

2. The method of paragraph 1, wherein the GHS is ibutamoren.

3. The method of paragraph 1, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

4. The method of paragraph 1, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

5. The method of paragraph 1, wherein the GLP-1 receptor agonist is semaglutide.

6. The method of paragraph 1, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

7. The method of paragraph 1, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

8. A pharmaceutical formulation, comprising:
   - a therapeutically effective amount of a GHS, or a pharmaceutically acceptable salt thereof;
   - a therapeutically effective amount of a GLP-1 receptor agonist or a dual GLP-1/GIP agonist, or a pharmaceutically acceptable salt individually thereof; and
   - a pharmaceutically acceptable carrier.

9. The pharmaceutical formulation of paragraph 8, wherein the GHS is ibutamoren.

10. The pharmaceutical formulation of paragraph 8, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

11. The pharmaceutical formulation of paragraph 8, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

12. The pharmaceutical formulation of paragraph 8, wherein the GLP-1 receptor agonist is semaglutide.

13. The pharmaceutical formulation of paragraph 8, wherein the therapeutically effective amount of GLP-1 receptor agonist is 1-200 mg.

14. The pharmaceutical formulation of paragraph 8, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

15. A method for maintaining lean muscle mass during obesity treatment, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) and a therapeutically effective amount of a glucagon-like peptide (GLP-1) receptor agonist, or a pharmaceutically acceptable salt individually thereof.

16. The method of paragraph 15, wherein the GHS is ibutamoren.

17. The method of paragraph 15, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

18. The method of paragraph 15, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

19. The method of paragraph 15, wherein the GLP-1 receptor agonist is semaglutide.

20. The method of paragraph 15, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

21. The method of paragraph 15, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

22. A method for maintaining lean muscle mass during treatment with a GLP-1 receptor agonist or a pharmaceutically acceptable salt thereof, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS), or a pharmaceutically acceptable salt thereof, simultaneously or sequentially with said GLP-1 receptor agonist.

23. The method of paragraph 22, wherein the GHS is ibutamoren.

24. The method of paragraph 22, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

25. The method of paragraph 22, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

26. The method of paragraph 22, wherein the GLP-1 receptor agonist is semaglutide.

27. The method of paragraph 22, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

28. The method of paragraph 22, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

29. A method for maintaining lean muscle mass during treatment with a GLP-1 receptor agonist or a dual GLP-1/GIP agonist, or a pharmaceutically acceptable salt individually thereof, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS), or a pharmaceutically acceptable salt thereof, simultaneously or sequentially with said a GLP-1 receptor agonist or a dual GLP-1/GIP agonist.

30. The method of paragraph 29, wherein the GHS is ibutamoren.

31. The method of paragraph 29, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

32. The method of paragraph 29, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

33. The method of paragraph 29, wherein the GLP-1 receptor agonist is semaglutide.

34. The method of paragraph 29, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

35. The method of paragraph 29, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

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Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.

WHAT IS CLAIMED IS:

1. A method for maintaining lean muscle mass during weight loss treatmennt, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) and a therapeutically effective amount of a glucagon-like peptide (GLP-1) receptor agonist, or a pharmaceutically acceptable salt individually thereof.

2. The method of claim 1, wherein the GHS is ibutamoren.

3. The method of claim 1, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

4. The method of claim 1, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

5. The method of claim 1, wherein the GLP-1 receptor agonist is semaglutide.

6. The method of claim 1, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

7. The method of claim 1, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

8. A pharmaceutical formulation, comprising:
   - a therapeutically effective amount of a GHS, or a pharmaceutically acceptable salt thereof;
   - a therapeutically effective amount of a GLP-1 receptor agonist or a dual GLP-1/GIP agonist, or a pharmaceutically acceptable salt individually thereof; and
   - a pharmaceutically acceptable carrier.

9. The pharmaceutical formulation of claim 8, wherein the GHS is ibutamoren.

10. The pharmaceutical formulation of claim 8, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

11. The pharmaceutical formulation of claim 8, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

12. The pharmaceutical formulation of claim 8, wherein the GLP-1 receptor agonist is semaglutide.

13. The pharmaceutical formulation of claim 8, wherein the therapeutically effective amount of GLP-1 receptor agonist is 1-200 mg.

14. The pharmaceutical formulation of claim 8, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

15. A method for maintaining lean muscle mass during obesity treatment, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) and a therapeutically effective amount of a glucagon-like peptide (GLP-1) receptor agonist, or a pharmaceutically acceptable salt individually thereof.

16. The method of claim 15, wherein the GHS is ibutamoren.

17. The method of claim 15, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

18. The method of claim 15, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

19. The method of claim 15, wherein the GLP-1 receptor agonist is semaglutide.

20. The method of claim 15, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

21. The method of claim 15, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

22. A method for maintaining lean muscle mass during treatment with a GLP-1 receptor agonist or a pharmaceutically acceptable salt thereof, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS), or a pharmaceutically acceptable salt thereof, simultaneously or sequentially with said GLP-1 receptor agonist.

23. The method of claim 22, wherein the GHS is ibutamoren.

24. The method of claim 22, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

25. The method of claim 22, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

26. The method of claim 22, wherein the GLP-1 receptor agonist is semaglutide.

27. The method of claim 22, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

28. The method of claim 22, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.

29. A method for maintaining lean muscle mass during treatment with a GLP-1 receptor agonist or a dual GLP-1/GIP agonist, or a pharmaceutically acceptable salt individually thereof,

comprising the step of administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS), or a pharmaceutically acceptable salt thereof, simultaneously or sequentially with said a GLP-1 receptor agonist or a dual GLP-1/GIP agonist.

30. The method of claim 29, wherein the GHS is ibutamoren.

31. The method of claim 29, wherein the therapeutically effective amount of ibutamoren is 10-50 mg.

32. The method of claim 29, wherein the GLP-1 receptor agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide or semaglutide.

33. The method of claim 29, wherein the GLP-1 receptor agonist is semaglutide.

34. The method of claim 29, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 1-200 mg.

35. The method of claim 29, wherein the therapeutically effective amount of the GLP-1 receptor agonist is 3-15 mg.