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(54) **Title:** HSP90 INHIBITORS FOR THE TREATMENT OF OBESITY AND METHODS OF USE THEREOF

(57) **Abstract:** HSP 90 inhibitors for the promotion of weight loss, as well as formulations containing these inhibitors and methods of using thereof, are described herein. Also provided are pharmaceutical compositions containing a therapeutically effective amount of a weight loss agent, or a pharmaceutically acceptable salt or prodrug thereof, in combination with one or more pharmaceutically acceptable excipients. The pharmaceutical compositions can be administered to induce weight loss in a pre-obese, obese, or morbidly obese patient, reduce body fat in a pre-obese, obese, or morbidly obese patient, reduce food intake in a pre-obese, obese, or morbidly obese patient, improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient, or combinations thereof. In particular embodiments, the weight loss agent is co-administered with leptin or a leptin analog.

HSP90 INHIBITORS FOR THE TREATMENT OF OBESITY AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims priority to U.S.S.N. 61/974,745, filed on April 3, 2014.

FIELD OF THE INVENTION

This invention is in the field of compounds, particularly HSP90 inhibitors, to regulate obesity, and methods of making and using thereof.

10 BACKGROUND OF THE INVENTION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Body mass index (BMI), a measurement which compares weight and height, 15 defines people as overweight (or pre-obese) if their BMI is between 25 and 30 kg/m², and obese when it is greater than 30 kg/m². Obesity is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and authorities view it as one of the most serious public health problems of the 21st century.

20 Obesity increases the risk of many physical and mental conditions. Excessive body weight is associated with various diseases, particularly cardiovascular diseases, diabetes mellitus type 2, obstructive sleep apnea, certain types of cancer, and osteoarthritis. As a result, obesity has been found to reduce life expectancy. These diseases are either directly caused by 25 obesity or indirectly related through mechanisms sharing a common cause such as a poor diet or a sedentary lifestyle. One of the strongest links is with type 2 diabetes. Excess body fat underlies 64% of cases of diabetes in men and 77% of cases in women. Increases in body fat alter the body's response to insulin, potentially leading to insulin resistance.

30 Obesity is one of the leading preventable causes of death worldwide. Obesity is most commonly caused by a combination of excessive energy intake, lack of physical activity, and genetic susceptibility, although a few

cases are caused primarily by genes, endocrine disorders, medications or psychiatric illness. Increasing rates of obesity at a societal level are felt to be due to an easily accessible and palatable diet, increased reliance on cars, and mechanized manufacturing. Since the discovery of leptin in 1994, many
5 other hormonal mechanisms have been elucidated that participate in the regulation of appetite and food intake, storage patterns of adipose tissue, and development of insulin resistance, including ghrelin, insulin, orexin, PYY 3-36, cholecystokinin, and adiponectin.

Adipokines are metabolic signal mediators produced by adipose
10 tissue; their action is important in the context of many obesity-related diseases. Leptin and ghrelin are considered to be complementary in their influence on appetite, with ghrelin produced by the stomach modulating short-term appetitive control (*i.e.*, to eat when the stomach is empty and to stop when the stomach is stretched). Leptin is produced by adipose tissue as
15 a signal of fat storage levels in the body, and mediates long-term appetitive controls (*i.e.*, to eat more when fat storages are low and less when fat storages are high). Although administration of leptin may be effective in a small subset of obese individuals who are leptin deficient, most obese individuals are thought to be leptin resistant and have been found to have
20 high levels of leptin. This resistance is thought to explain in part why administration of leptin has not been shown to be effective in suppressing appetite in most obese people.

While leptin and ghrelin are produced peripherally, they control appetite through their actions on the central nervous system. In particular,
25 they and other appetite-related hormones act on the hypothalamus, a region of the brain central to the regulation of food intake and energy expenditure. There are several circuits within the hypothalamus that contribute to its role in integrating appetite, the melanocortin pathway being the best understood. The circuit begins with the arcuate nucleus, an area of the hypothalamus that
30 has outputs to the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH), the brain's feeding and satiety centers, respectively.

The arcuate nucleus contains two distinct groups of neurons. The first group co-expresses neuropeptide Y (NPY) and agouti-related peptide (AgRP) and has stimulatory inputs to the LH and inhibitory inputs to the VMH. The second group co-expresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and has stimulatory
5 inputs to the VMH and inhibitory inputs to the LH. Consequently, NPY/AgRP neurons stimulate feeding and inhibit satiety, while POMC/CART neurons stimulate satiety and inhibit feeding. Both groups of arcuate nucleus neurons are regulated in part by leptin. Leptin inhibits the
10 NPY/AgRP group while stimulating the POMC/CART group. Thus a deficiency in leptin signaling, either via leptin deficiency or leptin resistance, leads to overfeeding. This may account for some genetic and acquired forms of obesity.

Dieting and physical exercise are the mainstays of treatment for
15 obesity. To supplement this, or in case of failure, anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption. In severe cases, surgery is performed or an intragastric balloon is placed to reduce stomach volume and/or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food. Maintaining this weight loss is frequently difficult and
20 often requires making exercise and a low calorie diet a permanent part of a person's lifestyle. Success rates of long-term weight loss maintenance with lifestyle changes are low, ranging from 2–20%.

A limited number of medications are available for the treatment of obesity. Concerns about side effects have diminished enthusiasm for
25 appetite-suppressant drugs, particularly fenfluramine, sibutramine, and phentermine, which carry serious risks and have been withdrawn from the market. Phentermine is approved only for short-term use. Orlistat (Xenical) is a medication that blocks the absorption of dietary fat and is also approved for longer-term use. However, it causes unpleasant side effects (greasy
30 stool), and requires supplementation with fat-soluble vitamins.

Although surgery (such as gastric bypass) is the last resort for the treatment of obesity, it can be extremely effective. However, it should be

performed at an experienced surgical center, because such operations can carry significant risks, especially in the post-operative period. Consensus recommendations are to limit surgical therapies to patients with morbid obesity (BMI > 40, BMI > 35 plus co-morbidities, or BMI > 30 with
 5 uncontrollable diabetes).

A number of weight-loss pills are available at local drugstores, supermarkets or health food stores. Even more options are available online. Most have not been proved effective, and some may be downright dangerous. Table 1 (below) shows common weight-loss pills and what the
 10 research shows about their effectiveness and safety.

Herbal extracts are often impure and contain so many different substances, that it is difficult to assess if the mixture as a whole is efficacious, much less what constitutes an effective dosage. With hundreds or more different compounds in the mixture, it could be more than one
 15 compound required for activity, or one compound inhibiting activity of another compound, so the source and processing of the original source material may result in an inactive or even dangerous product.

Table 1: Anecdotal Products for Weight Loss. Sources: U.S. Food and Drug Administration, 2010; Natural Medicines Comprehensive Database, 2010

Product	Claim	Effectiveness	Safety
Alli — OTC version of prescription drug orlistat (Xenical)	Decreases absorption of dietary fat	Effective; weight-loss amounts typically less for OTC versus prescription	FDA investigating reports of liver injury
Bitter orange	Increases calories burned	Insufficient reliable evidence to rate	Possibly unsafe
Chitosan	Blocks absorption of dietary fat	Insufficient reliable evidence to rate	Possibly safe

Chromium	Increases calories burned, decreases appetite and builds muscle	Insufficient reliable evidence to rate	Likely safe
Conjugated linoleic acid (CLA)	Reduces body fat and builds muscle	Possibly effective	Possibly safe
Country mallow (heartleaf)	Decreases appetite and increases calories burned	Insufficient reliable evidence to rate	Likely unsafe and banned by FDA
Ephedra	Decreases appetite	Possibly effective	Likely unsafe and banned by FDA
Green tea extract	Increases calorie and fat metabolism and decreases appetite	Insufficient reliable evidence to rate	Possibly safe
Guar gum	Blocks absorption of dietary fat and increases feeling of fullness	Possibly ineffective	Likely safe
Hoodia	Decreases appetite	Insufficient reliable evidence to rate	Insufficient information

It is therefore an object of the present invention to provide safe, well characterized and efficacious compounds for inducing weight loss, and methods of use thereof.

- 5 It is a further object of the present invention to provide an oral dosage form for the promotion of weight loss, and methods of use thereof.

SUMMARY OF THE INVENTION

HSP 90 inhibitors for the promotion of weight loss, as well as formulations containing these inhibitors and methods of using thereof, are described herein. Exemplary classes of inhibitors include, but are not limited to, xanthonoids (e.g., gambogic acid and derivatives thereof); benzoquinone ansamycin antibiotics (e.g., geldanamycin and derivatives thereof, such as tanespimycin, alvespimycin, retaspimycin, and IPI-493); resorcinol derivatives, such as ganetespib, NVP-AUY922, AT-13387, and KW-2478; purine analogs, such as BIIB021 (CNF 2024), MPC-3100, Debio 0932 (CUDC-305), PU-H71; and other compounds, such as SNX-5422, DS-2248, and XL-888. Also provided are pharmaceutical formulations containing a therapeutically effective amount of a weight loss agent, or a pharmaceutically acceptable salt or prodrug thereof, in combination with one or more pharmaceutically acceptable excipients. The pharmaceutical formulations can be administered to induce weight loss in a pre-obese, obese, or morbidly obese patient, reduce body fat in a pre-obese, obese, or morbidly obese patient, reduce food intake in a pre-obese, obese, or morbidly obese patient, improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient, or combinations thereof.

In particular embodiments, the weight loss agent is co-administered with leptin or a leptin analog, such as r-metHuLeptin (A-100, METRELEPTIN®), available from Amylin Pharmaceuticals (San Diego, Calif.).

In some cases, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to induce weight loss, preferably in a therapeutically effective amount and time of administration to decrease body mass or body fat by at least 10%, more preferably by at least 15%, most preferably by at least 20%, or higher.

In some cases, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to reduce food intake,

appetite, or combinations thereof, preferably in a therapeutically effective amount to reduce average daily food intake (in terms of calories) by at least 15%, more preferably by at least 25%, most preferably by at least 35%, or higher.

5 In some cases, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to improve glucose homeostasis, preferably in a therapeutically effective amount to reduce average fasting plasma blood glucose by at least 10%, more preferably by at
10 least 15%, most preferably by at least 20%, or higher. In cases where the pharmaceutical formulations are administered to normalize blood sugar, the formulations are preferably administered in an amount effective to lower blood glucose levels to less than about 180, 160, 140, 120, or 100 mg/dL. The formulations can be co-administered with other anti-diabetic therapies, if
15 necessary, to improve glucose homeostasis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a graph showing the decrease in percent body weight as a function of time (days) for vehicle and SR03 (0.5 mg/kg) in high fat diet (HFD) mice. Figure 1B is a graph showing food intake (g/animal/day) for
20 vehicle and SR03 (0.5 mg/kg) in HFD mice. Figure 1C is a graph showing percent body weight as a function of time (days) for vehicle and SR03 (0.5 mg/kg) in lean mice. Figure 1D is a graph showing food intake (g/animal/day) for vehicle and SR03 (0.5 mg/kg) in lean mice. Figure 1E is a graph showing the decrease in percent body weight as a function of time
25 (days) for vehicle and SR03 (0.5 mg/kg) in db/db mice. Figure 1F is a graph showing food intake (g/animal/day) for vehicle and SR03 (0.5 mg/kg) in db/db mice.

Figure 2A is a graph showing the decrease in percent body weight as a function of time (days) for AAG (15 mg/kg) in high fat diet (HFD) mice.
30 Figure 2B is a graph showing percent body weight as a function of time (days) for vehicle and AAG (15 mg/kg) in lean mice.

Figure 3A is a graph showing the decrease in percent body weight as a function of time (days) for AUY (15 mg/kg) in high fat diet (HFD) mice. Figure 3B is a graph showing percent body weight as a function of time (days) for vehicle and AUY(15 mg/kg) in lean mice.

5 **DETAILED DESCRIPTION OF THE INVENTION**

I. Definitions

"Hsp90", as used herein, includes each member of the family of heat shock proteins having a mass of about 90-kiloDaltons. For example, in humans the highly conserved Hsp90 family includes the cytosolic Hsp90 α and Hsp90 β isoforms, as well as GRP94, which is found in the endoplasmic reticulum, and HSP75/TRAP1, which is found in the mitochondrial matrix.

"HSP90 inhibitor", as used herein, refers to compounds that inhibit HSP90 and optionally preferably upregulate (e.g., increase levels of) HSP70.

"Analog" and "Derivative", are used herein interchangeably, and refer to a compound that possesses the same core as a parent compound, but differs from the parent compound in bond order, in the absence or presence of one or more atoms and/or groups of atoms, and combinations thereof. The derivative can differ from the parent compound, for example, in one or more substituents present on the core, which may include one or more atoms, functional groups, or substructures. The derivative can also differ from the parent compound in the bond order between atoms within the core. In general, a derivative can be imagined to be formed, at least theoretically, from the parent compound via chemical and/or physical processes.

"Co-administration", as used herein, includes simultaneous and sequential administration. An appropriate time course for sequential administration may be chosen by the physician, according to such factors as the nature of a patient's illness, and the patient's condition.

"Pharmaceutically acceptable", as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation,

allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

“Prodrug”, as used herein, refers to a pharmacological substance (drug) that is administered to a subject in an inactive (or significantly less
5 active) form. Once administered, the prodrug is metabolized in the body (*in vivo*) into a compound having the desired pharmacological activity.

“Alkyl”, as used herein, refers to the radical of saturated or unsaturated aliphatic groups, including straight-chain alkyl, alkenyl, or alkynyl groups, branched-chain alkyl, alkenyl, or alkynyl groups, cycloalkyl,
10 cycloalkenyl, or cycloalkynyl (alicyclic) groups, alkyl substituted cycloalkyl, cycloalkenyl, or cycloalkynyl groups, and cycloalkyl substituted alkyl, alkenyl, or alkynyl groups. Unless otherwise indicated, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), more preferably 20 or
15 fewer carbon atoms, more preferably 12 or fewer carbon atoms, and most preferably 8 or fewer carbon atoms. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure. The ranges provided above are inclusive of all values between the minimum value and the maximum value.

20 The term “alkyl” includes both “unsubstituted alkyls” and “substituted alkyls”, the latter of which refers to alkyl moieties having one or more substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents include, but are not limited to, halogen, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or
25 an acyl), thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, a phosphinate, amino, amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety.

30 Unless the number of carbons is otherwise specified, “lower alkyl” as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone

structure. Likewise, “lower alkenyl” and “lower alkynyl” have similar chain lengths. Preferred alkyl groups are lower alkyls.

The alkyl groups may also contain one or more heteroatoms within the carbon backbone. Preferably the heteroatoms incorporated into the
5 carbon backbone are oxygen, nitrogen, sulfur, and combinations thereof. In certain embodiments, the alkyl group contains between one and four heteroatoms.

“Alkenyl” and “Alkynyl”, as used herein, refer to unsaturated aliphatic groups containing one or more double or triple bonds analogous in
10 length (e.g., C₂-C₃₀) and possible substitution to the alkyl groups described above.

“Aryl”, as used herein, refers to 5-, 6- and 7-membered aromatic ring. The ring may be a carbocyclic, heterocyclic, fused carbocyclic, fused heterocyclic, bicarbocyclic, or biheterocyclic ring system, optionally
15 substituted by halogens, alkyl-, alkenyl-, and alkynyl-groups. Broadly defined, “Ar”, as used herein, includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the
20 like. Those aryl groups having heteroatoms in the ring structure may also be referred to as “heteroaryl”, “aryl heterocycles”, or “heteroaromatics”. The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl,
25 imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, --CF₃, --CN, or the like. The term “Ar” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are
30 “fused rings”) wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocycles. Examples of heterocyclic ring include, but are not limited to,

benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl,
 benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl,
 benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH
 carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny,
 5 decahydroquinoliny, 2*H*,6*H*-1,5,2-dithiaziny, dihydrofuro[2,3
 b]tetrahydrofuran, furanyl, furazanyl, imidazolidiny, imidazoliny,
 imidazolyl, 1*H*-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3*H*-
 indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny,
 isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl,
 10 morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-
 oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
 oxazolidiny, oxazolyl, oxindolyl, pyrimidiny, phenanthridiny,
 phenanthroliny, phenaziny, phenothiaziny, phenoxathiny, phenoxaziny,
 phthalaziny, piperaziny, piperidiny, piperidonyl, 4-piperidonyl, piperonyl,
 15 pteridiny, puriny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl,
 pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny,
 pyridyl, pyrimidiny, pyrrolidiny, pyrroliny, 2*H*-pyrrolyl, pyrrolyl,
 quinazoliny, quinoliny, 4*H*-quinoliziny, quinoxaliny, quinuclidiny,
 tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl,
 20 6*H*-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-
 thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl,
 thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl and xanthenyl.

“Alkylaryl”, as used herein, refers to an alkyl group substituted with
 an aryl group (e.g., an aromatic or hetero aromatic group).

25 “Heterocycle” or “heterocyclic”, as used herein, refers to a cyclic
 radical attached via a ring carbon or nitrogen of a monocyclic or bicyclic
 ring containing 3-10 ring atoms, and preferably from 5-6 ring atoms,
 consisting of carbon and one to four heteroatoms each selected from the
 group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is
 30 absent or is H, O, (C₁₋₄) alkyl, phenyl or benzyl, and optionally containing
 one or more double or triple bonds, and optionally substituted with one or
 more substituents. The term “heterocycle” also encompasses substituted and

unsubstituted heteroaryl rings. Examples of heterocyclic ring include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4*aH*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazoliny, quinolinyl, 4*H*-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl and xanthenyl.

“Heteroaryl”, as used herein, refers to a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and 1, 2, 3, or 4 heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) where Y is absent or is H, O, (C₁-C₈) alkyl, phenyl or benzyl. Non-limiting examples of heteroaryl groups include furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide), quinolyl

(or its N-oxide) and the like. The term "heteroaryl" can include radicals of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto. Examples of
5 heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl (or its N-oxide), thientyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide), quinolyl (or its N-oxide), and the like.

“Halogen”, as used herein, refers to fluorine, chlorine, bromine, or
10 iodine.

The term “substituted” as used herein, refers to all permissible substituents of the compounds described herein. In the broadest sense, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic
15 substituents of organic compounds. Illustrative substituents include, but are not limited to, halogens, hydroxyl groups, or any other organic groupings containing any number of carbon atoms, preferably 1-14 carbon atoms, and optionally include one or more heteroatoms such as oxygen, sulfur, or nitrogen grouping in linear, branched, or cyclic structural formats.
20 Representative substituents include alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxyl, alkoxy, substituted alkoxy, phenoxy, substituted phenoxy, aroxy, substituted aroxy, alkylthio, substituted alkylthio, phenylthio, substituted phenylthio,
25 arylthio, substituted arylthio, cyano, isocyano, substituted isocyano, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted amido, sulfonyl, substituted sulfonyl, sulfonic acid, phosphoryl, substituted phosphoryl, phosphonyl, substituted phosphonyl, polyaryl, substituted polyaryl, C₃-C₂₀ cyclic, substituted C₃-C₂₀
30 cyclic, heterocyclic, substituted heterocyclic, aminoacid, peptide, and polypeptide groups.

Heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. It is understood that “substitution” or “substituted” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.* a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

“Obese,” as used herein, refers to a patient having a body mass index of greater than 30 kg/m². “Overweight” and “Pre-Obese,” as used herein, refer to patients having a body mass index of greater than 25 kg/m².

“Morbidly Obese,” as used herein, refers to a patient having a body mass index of greater than 40 kg/m², a body mass index of greater than 35 kg/m² in combination with one or more co-morbidities, a body mass index of greater than 30 kg/m² in combination with uncontrollable diabetes, or combinations thereof.

“Effective amount” or “therapeutically effective amount”, as used herein, refers to an amount of a weight loss agent that is effective to induce weight loss in a pre-obese, obese, or morbidly obese patient, reduce body fat in a pre-obese, obese, or morbidly obese patient, reduce food intake in a pre-obese, obese, or morbidly obese patient, improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient, prevent weight gain and/or prevent an increase in body mass index in a normal, pre-obese, obese, or morbidly obese patient, or combinations thereof.

The weight loss agent can also be a pharmaceutically acceptable salt of any of the compounds described above. In some cases, it may be desirable to prepare the salt of a compound described above due to one or more of the salt's advantageous physical properties, such as enhanced stability or a desirable solubility or dissolution profile.

Generally, pharmaceutically acceptable salts can be prepared by reaction of the free acid or base forms of a compound described above with a stoichiometric amount of the appropriate base or acid in water, in an organic

solvent, or in a mixture of the two. Generally, non-aqueous media including ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, p. 704; and
5 "Handbook of Pharmaceutical Salts: Properties, Selection, and Use," P. Heinrich Stahl and Camille G. Wermuth, Eds., Wiley-VCH, Weinheim, 2002.

Suitable pharmaceutically acceptable acid addition salts include those derived from inorganic acids, such as hydrochloric, hydrobromic,
10 hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and
15 trifluoroacetic acids.

Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate,
20 digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, *p*-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate,
25 cyclohexylaminosulfonate, algenic acid, β -hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and
30 undecanoate.

In some cases, the pharmaceutically acceptable salt may include alkali metal salts, including sodium or potassium salts; alkaline earth metal

salts, *e.g.*, calcium or magnesium salts; and salts formed with suitable organic ligands, *e.g.*, quaternary ammonium salts. Base salts can also be formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, 5 meglumine, olamine, tromethamine and zinc salts.

Organic salts may be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic 10 nitrogen-containing groups may also be quaternized with agents such as lower alkyl (C₁-C₆) halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (*e.g.*, benzyl and 15 phenethyl bromides), and others.

The weight loss agent can also be a pharmaceutically acceptable prodrug of any of the compounds described above. Prodrugs are compounds that, when metabolized *in vivo*, undergo conversion to compounds having the desired pharmacological activity. Prodrugs can be prepared by replacing 20 appropriate functionalities present in the compounds described above with "pro-moieties" as described, for example, in H. Bundgaard, Design of Prodrugs (1985). Examples of prodrugs include ester, ether or amide derivatives of the compounds described above, polyethylene glycol derivatives of the compounds described above, N-acyl amine derivatives, 25 dihydropyridine pyridine derivatives, amino-containing derivatives conjugated to polypeptides, 2-hydroxybenzamide derivatives, carbamate derivatives, N-oxides derivatives that are biologically reduced to the active amines, and N-mannich base derivatives. For further discussion of prodrugs, *see*, for example, Rautio, J. *et al. Nature Reviews Drug Discovery*. 7:255-270 30 (2008).

II. HSP90 Inhibitors

HSP90 inhibitors that can be administered to promote weight loss, reduce body fat, reduce food intake, improve glucose homeostasis, or combinations thereof are provided herein.

5 Heat shock proteins (HSPs) are a class of chaperone proteins that are up-regulated in response to elevated temperature and other environmental stresses, such as ultraviolet light, nutrient deprivation and oxygen deprivation. HSPs act as chaperones to other cellular proteins (called client proteins), facilitate their proper folding and repair and aid in the refolding of
10 misfolded client proteins. There are several known families of HSPs, each having its own set of client proteins. The Hsp90 family is one of the most abundant HSP families accounting for about 1-2% of proteins in a cell that is not under stress and increasing to about 4-6% in a cell under stress. Inhibition of Hsp90 results in the degradation of its client proteins via the
15 ubiquitin proteasome pathway. Unlike other chaperone proteins, the client proteins of Hsp90 are mostly protein kinases or transcription factors involved in signal transduction.

Suitable classes of HSP90 inhibitors include xanthonoids (e.g., gambogic acid and derivatives thereof (e.g., C(34) and C(39) derivatives);
20 benzoquinone ansamycin antibiotics (e.g., geldanamycin and derivatives thereof, such as tanespimycin, alvespimycin, retaspimycin, and IPI-493); resorcinol derivatives, such as ganetespib, NVP-AUY922, AT-13387, and KW-2478; purine analogs, such as BIIB021 (CNF 2024), MPC-3100, Debio
25 0932 (CUDC-305), PU-H71; other compounds, such as SNX-5422, DS-2248, and XL-888; imidazole compounds, such as those described in U.S. Patent Nos. 8,629,285; hydrazonamide compounds, such as those described in U.S. Patent No. 8,648,071; diazinone and triazinone compounds such as those described in U.S. Patent No. 8,524,712; pyrrole compounds such as those described in U.S. Patent No. 8,450,500; pyrazole compounds, such as
30 those described in 8,329,899; and triazole compounds such as those described in U.S. Patent No. 8,106,083.

In particular embodiments, the compound inhibit HSP90 and upregulate HSP70.

The weight loss agents may have one or more chiral centers, and thus exist as one or more stereoisomers. Such stereoisomers can exist as a single
5 enantiomer, a mixture of enantiomers, a mixture of diastereomers, or a racemic mixture.

As used herein, the term “stereoisomers” refers to compounds made up of the same atoms having the same bond order but having different three-dimensional arrangements of atoms that are not interchangeable. The three-
10 dimensional structures are called configurations. As used herein, the term “enantiomers” refers to two stereoisomers that are non-superimposable mirror images of one another. As used herein, the term “optical isomer” is equivalent to the term “enantiomer”. As used herein the term “diastereomer” refers to two stereoisomers which are not mirror images but also not
15 superimposable. The terms “racemate”, “racemic mixture” or “racemic modification” refer to a mixture of equal parts of enantiomers. The term “chiral center” refers to a carbon atom to which four different groups are attached. Choice of the appropriate chiral column, eluent, and conditions necessary to effect separation of the pair of enantiomers is well known to one
20 of ordinary skill in the art using standard techniques (see e.g. Jacques, J. et al., “Enantiomers, Racemates, and Resolutions”, John Wiley and Sons, Inc. 1981).

The weight loss agent can also be a pharmaceutically acceptable salt of any of the compounds described above. In some cases, it may be
25 desirable to prepare the salt of a compound described above due to one or more of the salt's advantageous physical properties, such as enhanced stability or a desirable solubility or dissolution profile.

Generally, pharmaceutically acceptable salts can be prepared by reaction of the free acid or base forms of a compound described above with a
30 stoichiometric amount of the appropriate base or acid in water, in an organic solvent, or in a mixture of the two. Generally, non-aqueous media including ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists

of suitable salts are found in Remington's Pharmaceutical Sciences, 20th ed.,
Lippincott Williams & Wilkins, Baltimore, MD, 2000, p. 704; and
"Handbook of Pharmaceutical Salts: Properties, Selection, and Use," P.
Heinrich Stahl and Camille G. Wermuth, Eds., Wiley-VCH, Weinheim,
5 2002.

Suitable pharmaceutically acceptable acid addition salts include those
derived from inorganic acids, such as hydrochloric, hydrobromic,
hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric,
carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic,
10 benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic,
isothionic, lactic, lactobionic, maleic, malic, methanesulfonic,
trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and
trifluoroacetic acids.

Suitable organic acids generally include, for example, aliphatic,
15 cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic
classes of organic acids. Specific examples of suitable organic acids include
acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate,
digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate,
maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid,
20 mesylate, stearate, salicylate, *p*-hydroxybenzoate, phenylacetate, mandelate,
embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate,
pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate,
cyclohexylaminosulfonate, algenic acid, β -hydroxybutyric acid, galactarate,
galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate,
25 cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate,
heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate,
pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and
undecanoate.

In some cases, the pharmaceutically acceptable salt may include
30 alkali metal salts, including sodium or potassium salts; alkaline earth metal
salts, *e.g.*, calcium or magnesium salts; and salts formed with suitable
organic ligands, *e.g.*, quaternary ammonium salts. Base salts can also be

formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts may be made from secondary, tertiary or quaternary
5 amine salts, such as tromethamine, diethylamine, N,N'-
dibenzylethylenediamine, chlorprocaine, choline, diethanolamine,
ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic
nitrogen-containing groups may also be quaternized with agents such as
10 lower alkyl (C₁-C₆) halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides,
bromides, and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and
diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl, and stearyl
chlorides, bromides, and iodides), arylalkyl halides (*e.g.*, benzyl and
phenethyl bromides), and others.

The weight loss agent can also be a pharmaceutically acceptable
15 prodrug of any of the compounds described above. Prodrugs are compounds
that, when metabolized *in vivo*, undergo conversion to compounds having the
desired pharmacological activity. Prodrugs can be prepared by replacing
appropriate functionalities present in the compounds described above with
"pro-moieties" as described, for example, in H. Bundgaard, Design of
20 Prodrugs (1985). Examples of prodrugs include ester, ether or amide
derivatives of the compounds described above, polyethylene glycol
derivatives of the compounds described above, N-acyl amine derivatives,
dihydropyridine pyridine derivatives, amino-containing derivatives
conjugated to polypeptides, 2-hydroxybenzamide derivatives, carbamate
25 derivatives, N-oxides derivatives that are biologically reduced to the active
amines, and N-mannich base derivatives. For further discussion of prodrugs,
see, for example, Rautio, J. *et al. Nature Reviews Drug Discovery*. 7:255-270
(2008).

III. Pharmaceutical Formulations

30 Pharmaceutical formulations are provided containing a
therapeutically effective amount of a weight loss agent described herein, or a
pharmaceutically acceptable salt or prodrug thereof, in combination with one

or more pharmaceutically acceptable excipients. Representative excipients include solvents, diluents, pH modifying agents, preservatives, antioxidants, suspending agents, wetting agents, viscosity modifiers, tonicity agents, stabilizing agents, and combinations thereof. Suitable pharmaceutically acceptable excipients are preferably selected from materials that are generally recognized as safe (GRAS), and may be administered to an individual without causing undesirable biological side effects or unwanted interactions.

A. Additional Therapeutics

In some cases, the pharmaceutical formulation can further contain one or more additional active agents.

In certain embodiments, the pharmaceutical formulations further contain leptin, a leptin analog, or combinations thereof.

Leptin is a peptide hormone that serves as the afferent signal in a negative feedback loop regulating food intake and body weight *in vivo*. Unprocessed human leptin is synthesized *in vivo* as a 167 amino acid, 16 kDa protein prohormone. Unprocessed leptin includes an N-terminal 21-amino acid signal sequence that is cleaved from the remainder of the polypeptide to generate mature, circulating, leptin (containing 146 amino acids).

The terms “leptin” and “leptin analog,” as used herein, encompass naturally occurring human leptin, naturally occurring leptin produced by a non-human species such as a mouse or rat, recombinantly produced mature leptin, such as metreleptin (*i.e.*, recombinant methionyl human leptin or r-metHuLeptin, which is a 147 amino acid leptin analog generated by the genetically engineered N-terminal addition of a methionine to the N-terminal amino acid of the 146-amino acid, mature, circulating, human leptin), as well as leptin fragments, leptin variants, leptin fusion proteins, and other derivatives thereof known in the art to possess biological activity.

Exemplary leptin analogs and derivatives include those described in International Patent Publication Nos. WO 96/05309, WO 96/40912; WO 97/06816, WO 00/20872, WO 97/18833, WO 97/38014, WO 98/08512, WO

98/12224, WO 98/28427, WO 98/46257, WO 98/55139, WO 00/09165, WO
00/47741, WO 2004/039832, WO 97/02004, and WO 00/21574;
International Patent Applicant Nos. PCT/US96/22308 and PCT/US96/01471;
U.S. Patent Nos. 5,521,283, 5,532,336, 5,552,524, 5,552,523, 5,552,522,
5 5,935,810, 6,001,968, 6,429,290, 6,350,730, 6,936,439, 6,420,339,
6,541,033, 7,112,659, 7,183,254, and 7,208,577, and U.S. Patent Publication
Nos. 2005/0176107, 2005/0163799. Exemplary leptin variants include those
where the amino acid at position 43 is substituted with Asp or Glu; position
48 is substituted Ala; position 49 is substituted with Glu, or absent; position
10 75 is substituted with Ala; position 89 is substituted with Leu; position 93 is
substituted with Asp or Glu; position 98 is substituted with Ala; position 117
is substituted with Ser, position 139 is substituted with Leu, position 167 is
substituted with Ser, and any combination thereof.

In certain embodiments, the pharmaceutical formulation includes r-
15 metHuLeptin (A-100, METRELEPTIN®), available from Amylin
Pharmaceuticals (San Diego, Calif.).

Pharmaceutical formulations can also include one or more vitamins,
minerals, dietary supplements, nutraceutical agents, such as proteins,
carbohydrates, amino acids, fatty acids, antioxidants, and plant or animal
20 extracts, or combinations thereof. Suitable vitamins, minerals, nutraceutical
agents, and dietary supplements are known in the art, and disclosed, for
example, in Roberts *et al.*, (*Nutraceuticals: The Complete Encyclopedia of
Supplements, Herbs, Vitamins, and Healing Foods*, American Nutraceutical
Association, 2001). Nutraceutical agents and dietary supplements are also
25 disclosed in *Physicians' Desk Reference for Nutritional Supplements*, 1st Ed.
(2001) and *The Physicians' Desk Reference for Herbal Medicines*, 1st Ed.
(2001).

B. Enteral Formulations

Suitable oral dosage forms include tablets, capsules, solutions,
30 suspensions, syrups, and lozenges. Tablets can be made using compression
or molding techniques well known in the art. Gelatin or non-gelatin capsules

can prepared as hard or soft capsule shells, which can encapsulate liquid, solid, and semi-solid fill materials, using techniques well known in the art.

Formulations may be prepared using one or more pharmaceutically acceptable excipients, including diluents, preservatives, binders, lubricants, 5 disintegrators, swelling agents, fillers, stabilizers, and combinations thereof.

Excipients, including plasticizers, pigments, colorants, stabilizing agents, and glidants, may also be used to form coated compositions for enteral administration. Delayed release dosage formulations may be prepared as described in standard references such as "Pharmaceutical dosage form tablets", eds. Liberman *et. al.* (New York, Marcel Dekker, Inc., 1989), 10 "Remington – The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et al., (Media, PA: Williams and Wilkins, 1995). These references provide information on 15 excipients, materials, equipment and process for preparing tablets and capsules and delayed release dosage forms of tablets, capsules, and granules.

Examples of suitable coating materials include, but are not limited to, cellulose polymers such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose 20 phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name EUDRAGIT® (Roth Pharma, Westerstadt, Germany), zein, shellac, and polysaccharides.

Diluents, also referred to as "fillers," are typically necessary to 25 increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets or formation of beads and granules. Suitable diluents include, but are not limited to, dicalcium phosphate dihydrate, calcium sulfate, lactose, sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed 30 starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar.

Binders are used to impart cohesive qualities to a solid dosage formulation, and thus ensure that a tablet or bead or granule remains intact after the formation of the dosage forms. Suitable binder materials include, but are not limited to, starch, pregelatinized starch, gelatin, sugars (including
5 sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia, tragacanth, sodium alginate, cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl
10 methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone.

Lubricants are used to facilitate tablet manufacture. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, glycerol behenate, polyethylene glycol, talc,
15 and mineral oil.

Disintegrants are used to facilitate dosage form disintegration or "breakup" after administration, and generally include, but are not limited to, starch, sodium starch glycolate, sodium carboxymethyl starch, sodium carboxymethylcellulose, hydroxypropyl cellulose, pregelatinized starch,
20 clays, cellulose, alginate, gums or cross linked polymers, such as cross-linked PVP (Polyplasdone® XL from GAF Chemical Corp).

Stabilizers are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions. Suitable stabilizers include, but are not limited to, antioxidants, butylated hydroxytoluene
25 (BHT); ascorbic acid, its salts and esters; Vitamin E, tocopherol and its salts; sulfites such as sodium metabisulphite; cysteine and its derivatives; citric acid; propyl gallate, and butylated hydroxyanisole (BHA).

1. Controlled release formulations

Oral dosage forms, such as capsules, tablets, solutions, and
30 suspensions, can be formulated for controlled release. For example, the one or more compounds and optional one or more additional active agents can be formulated into nanoparticles, microparticles, and combinations thereof, and

encapsulated in a soft or hard gelatin or non-gelatin capsule or dispersed in a dispersing medium to form an oral suspension or syrup. The particles can be formed of the drug and a controlled release polymer or matrix.

Alternatively, the drug particles can be coated with one or more controlled
5 release coatings prior to incorporation in to the finished dosage form.

In another embodiment, the one or more compounds and optional one or more additional active agents are dispersed in a matrix material, which gels or emulsifies upon contact with an aqueous medium, such as physiological fluids. In the case of gels, the matrix swells entrapping the
10 active agents, which are released slowly over time by diffusion and/or degradation of the matrix material. Such matrices can be formulated as tablets or as fill materials for hard and soft capsules.

In still another embodiment, the one or more compounds, and optional one or more additional active agents are formulated into a solid oral
15 dosage form, such as a tablet or capsule, and the solid dosage form is coated with one or more controlled release coatings, such as a delayed release coatings or extended release coatings. The coating or coatings may also contain the compounds and/or additional active agents.

Extended release formulations

20 The extended release formulations are generally prepared as diffusion or osmotic systems, for example, as described in "Remington – The science and practice of pharmacy" (20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000). A diffusion system typically consists of two types of devices, a reservoir and a matrix, and is well known and described in the art.
25 The matrix devices are generally prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet form. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and
30 polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkylcelluloses such as hydroxypropyl-cellulose,

hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor
5 oil or hydrogenated vegetable oil, or mixtures thereof.

In certain embodiments, the plastic material is a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl
10 methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In certain embodiments, the acrylic polymer is comprised of one or more
15 ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In one embodiment, the acrylic polymer is an acrylic resin lacquer
20 such as that which is commercially available from Rohm Pharma under the tradename EUDRAGIT®. In further preferred embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the tradenames EUDRAGIT® RL30D and EUDRAGIT® RS30D, respectively. EUDRAGIT® RL30D and
25 EUDRAGIT® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in EUDRAGIT® RL30D and 1:40 in EUDRAGIT® RS30D. The mean molecular weight is about 150,000. EUDRAGIT® S-100 and
30 EUDRAGIT® L-100 are also preferred. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. EUDRAGIT® RL/RS mixtures are insoluble in water and in

digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

The polymers described above such as EUDRAGIT® RL/RS may be mixed together in any desired ratio in order to ultimately obtain a sustained-
5 release formulation having a desirable dissolution profile. Desirable sustained-release multiparticulate systems may be obtained, for instance, from 100% EUDRAGIT®RL, 50% EUDRAGIT® RL and 50% EUDRAGIT® RS, and 10% EUDRAGIT® RL and 90% EUDRAGIT® RS. One skilled in the art will recognize that other acrylic polymers may also be
10 used, such as, for example, EUDRAGIT®L.

Alternatively, extended release formulations can be prepared using osmotic systems or by applying a semi-permeable coating to the dosage form. In the latter case, the desired drug release profile can be achieved by combining low permeable and high permeable coating materials in suitable
15 proportion.

The devices with different drug release mechanisms described above can be combined in a final dosage form comprising single or multiple units. Examples of multiple units include, but are not limited to, multilayer tablets and capsules containing tablets, beads, or granules. An immediate release
20 portion can be added to the extended release system by means of either applying an immediate release layer on top of the extended release core using a coating or compression process or in a multiple unit system such as a capsule containing extended and immediate release beads.

Extended release tablets containing hydrophilic polymers are
25 prepared by techniques commonly known in the art such as direct compression, wet granulation, or dry granulation. Their formulations usually incorporate polymers, diluents, binders, and lubricants as well as the active pharmaceutical ingredient. The usual diluents include inert powdered substances such as starches, powdered cellulose, especially crystalline and
30 microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium

phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders include substances such as starch, gelatin and sugars such as lactose, fructose, and glucose. Natural and synthetic gums, including acacia, 5 alginates, methylcellulose, and polyvinylpyrrolidone can also be used. Polyethylene glycol, hydrophilic polymers, ethylcellulose and waxes can also serve as binders. A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, 10 stearic acid and hydrogenated vegetable oils.

Extended release tablets containing wax materials are generally prepared using methods known in the art such as a direct blend method, a congealing method, and an aqueous dispersion method. In the congealing method, the drug is mixed with a wax material and either spray- congealed or 15 congealed and screened and processed.

Delayed release formulations

Delayed release formulations can be created by coating a solid dosage form with a polymer film, which is insoluble in the acidic environment of the stomach, and soluble in the neutral environment of the 20 small intestine.

The delayed release dosage units can be prepared, for example, by coating a drug or a drug-containing composition with a selected coating material. The drug-containing composition may be, e.g., a tablet for incorporation into a capsule, a tablet for use as an inner core in a "coated 25 core" dosage form, or a plurality of drug-containing beads, particles or granules, for incorporation into either a tablet or capsule. Preferred coating materials include bioerodible, gradually hydrolyzable, gradually water-soluble, and/or enzymatically degradable polymers, and may be conventional "enteric" polymers. Enteric polymers, as will be appreciated by those skilled 30 in the art, become soluble in the higher pH environment of the lower gastrointestinal tract or slowly erode as the dosage form passes through the gastrointestinal tract, while enzymatically degradable polymers are degraded

by bacterial enzymes present in the lower gastrointestinal tract, particularly in the colon. Suitable coating materials for effecting delayed release include, but are not limited to, cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl
5 cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, methylcellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl
10 acrylate, methyl methacrylate and/or ethyl methacrylate, and other methacrylic resins that are commercially available under the tradename EUDRAGIT[®] (Rohm Pharma; Westerstadt, Germany), including EUDRAGIT[®] L30D-55 and L100-55 (soluble at pH 5.5 and above), EUDRAGIT[®] L-100 (soluble at pH 6.0 and above), EUDRAGIT[®] S
15 (soluble at pH 7.0 and above, as a result of a higher degree of esterification), and EUDRAGITs[®] NE, RL and RS (water-insoluble polymers having different degrees of permeability and expandability); vinyl polymers and copolymers such as polyvinyl pyrrolidone, vinyl acetate, vinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate
20 copolymer; enzymatically degradable polymers such as azo polymers, pectin, chitosan, amylose and guar gum; zein and shellac. Combinations of different coating materials may also be used. Multi-layer coatings using different polymers may also be applied.

The preferred coating weights for particular coating materials may be
25 readily determined by those skilled in the art by evaluating individual release profiles for tablets, beads and granules prepared with different quantities of various coating materials. It is the combination of materials, method and form of application that produce the desired release characteristics, which one can determine only from the clinical studies.

30 The coating composition may include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc. A plasticizer is normally present to reduce the fragility of the coating, and will

generally represent about 10 wt. % to 50 wt. % relative to the dry weight of the polymer. Examples of typical plasticizers include polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl

5 citrate, castor oil and acetylated monoglycerides. A stabilizing agent is preferably used to stabilize particles in the dispersion. Typical stabilizing agents are nonionic emulsifiers such as sorbitan esters, polysorbates and polyvinylpyrrolidone. Glidants are recommended to reduce sticking effects during film formation and drying, and will generally represent approximately

10 25 wt. % to 100 wt. % of the polymer weight in the coating solution. One effective glidant is talc. Other glidants such as magnesium stearate and glycerol monostearates may also be used. Pigments such as titanium dioxide may also be used. Small quantities of an anti-foaming agent, such as a silicone (e.g., simethicone), may also be added to the coating composition.

Pulsatile Release

The formulation can provide pulsatile delivery of the one or more of the compounds disclosed herein. By "pulsatile" is meant that a plurality of drug doses are released at spaced apart intervals of time. Generally, upon
5 ingestion of the dosage form, release of the initial dose is substantially immediate, i.e., the first drug release "pulse" occurs within about one hour of ingestion. This initial pulse is followed by a first time interval (lag time) during which very little or no drug is released from the dosage form, after which a second dose is then released. Similarly, a second nearly drug
10 release-free interval between the second and third drug release pulses may be designed. The duration of the nearly drug release-free time interval will vary depending upon the dosage form design e.g., a twice daily dosing profile, a three times daily dosing profile, etc. For dosage forms providing a twice daily dosage profile, the nearly drug release-free interval has a duration of
15 approximately 3 hours to 14 hours between the first and second dose. For dosage forms providing a three times daily profile, the nearly drug release-free interval has a duration of approximately 2 hours to 8 hours between each of the three doses.

In one embodiment, the pulsatile release profile is achieved with
20 dosage forms that are closed and preferably sealed capsules housing at least two drug-containing "dosage units" wherein each dosage unit within the capsule provides a different drug release profile. Control of the delayed release dosage unit(s) is accomplished by a controlled release polymer coating on the dosage unit, or by incorporation of the active agent in a
25 controlled release polymer matrix. Each dosage unit may comprise a compressed or molded tablet, wherein each tablet within the capsule provides a different drug release profile. For dosage forms mimicking a twice a day dosing profile, a first tablet releases drug substantially immediately following ingestion of the dosage form, while a second tablet
30 releases drug approximately 3 hours to less than 14 hours following ingestion of the dosage form. For dosage forms mimicking a three times daily dosing profile, a first tablet releases drug substantially immediately

following ingestion of the dosage form, a second tablet releases drug approximately 3 hours to less than 10 hours following ingestion of the dosage form, and the third tablet releases drug at least 5 hours to approximately 18 hours following ingestion of the dosage form. It is possible that the dosage form includes more than three tablets. While the dosage form will not generally include more than a third tablet, dosage forms housing more than three tablets can be utilized.

Alternatively, each dosage unit in the capsule may comprise a plurality of drug-containing beads, granules or particles. As is known in the art, drug-containing "beads" refer to beads made with drug and one or more excipients or polymers. Drug-containing beads can be produced by applying drug to an inert support, e.g., inert sugar beads coated with drug or by creating a "core" comprising both drug and one or more excipients. As is also known, drug-containing "granules" and "particles" comprise drug particles that may or may not include one or more additional excipients or polymers. In contrast to drug-containing beads, granules and particles do not contain an inert support. Granules generally comprise drug particles and require further processing. Generally, particles are smaller than granules, and are not further processed. Although beads, granules and particles may be formulated to provide immediate release, beads and granules are generally employed to provide delayed release.

C. Parenteral Formulations

The compounds can be formulated for parenteral administration. "Parenteral administration", as used herein, means administration by any method other than through the digestive tract or non-invasive topical or regional routes. For example, parenteral administration may include administration to a patient intravenously, intradermally, intraperitoneally, intrapleurally, intratracheally, intramuscularly, subcutaneously, by injection, and by infusion.

Parenteral formulations can be prepared as aqueous compositions using techniques is known in the art. Typically, such compositions can be prepared as injectable formulations, for example, solutions or suspensions;

solid forms suitable for using to prepare solutions or suspensions upon the addition of a reconstitution medium prior to injection; emulsions, such as water-in-oil (w/o) emulsions, oil-in-water (o/w) emulsions, and microemulsions thereof, liposomes, or emulsomes.

5 The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, one or more polyols (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), oils, such as vegetable oils (e.g., peanut oil, corn oil, sesame oil, etc.), and combinations thereof. The proper fluidity can be maintained, for example, by the use of a coating, such as
10 lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

 Solutions and dispersions of the active compounds as the free acid or base or pharmacologically acceptable salts thereof can be prepared in water
15 or another solvent or dispersing medium suitably mixed with one or more pharmaceutically acceptable excipients including, but not limited to, surfactants, dispersants, emulsifiers, pH modifying agents, and combination thereof.

 Suitable surfactants may be anionic, cationic, amphoteric or nonionic
20 surface active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions. Examples of anionic surfactants include sodium, potassium, ammonium of long chain alkyl sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium dodecylbenzene
25 sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylthioxyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited to, quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethylbenzyl ammonium chloride,
30 polyoxyethylene and coconut amine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate,

sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, polyoxyethylene monolaurate, polysorbates, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, Poloxamer[®] 401, stearyl monoisopropanolamide, and polyoxyethylene
5 hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl- β -alanine, sodium N-lauryl- β -iminodipropionate, myristoamphoacetate, lauryl betaine and lauryl sulfobetaine.

The formulation can contain a preservative to prevent the growth of microorganisms. Suitable preservatives include, but are not limited to,
10 parabens, chlorobutanol, phenol, sorbic acid, and thimerosal. The formulation may also contain an antioxidant to prevent degradation of the active agent(s).

The formulation is typically buffered to a pH of 3-8 for parenteral administration upon reconstitution. Suitable buffers include, but are not
15 limited to, phosphate buffers, acetate buffers, and citrate buffers.

Water soluble polymers are often used in formulations for parenteral administration. Suitable water-soluble polymers include, but are not limited to, polyvinylpyrrolidone, dextran, carboxymethylcellulose, and polyethylene glycol.

20 Sterile injectable solutions can be prepared by incorporating the active compounds in the required amount in the appropriate solvent or dispersion medium with one or more of the excipients listed above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a
25 sterile vehicle which contains the basic dispersion medium and the required other ingredients from those listed above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a
30 previously sterile-filtered solution thereof. The powders can be prepared in such a manner that the particles are porous in nature, which can increase

dissolution of the particles. Methods for making porous particles are well known in the art.

1. Controlled release formulations

The parenteral formulations described herein can be formulated for controlled release including immediate release, delayed release, extended release, pulsatile release, and combinations thereof.

Nano- and microparticles

For parenteral administration, the compounds, and optionally one or more additional active agents, can be incorporated into microparticles, nanoparticles, or combinations thereof that provide controlled release. In embodiments wherein the formulations contains two or more drugs, the drugs can be formulated for the same type of controlled release (e.g., delayed, extended, immediate, or pulsatile) or the drugs can be independently formulated for different types of release (e.g., immediate and delayed, immediate and extended, delayed and extended, delayed and pulsatile, etc.).

For example, the compounds and/or one or more additional active agents can be incorporated into polymeric microparticles that provide controlled release of the drug(s). Release of the drug(s) is controlled by diffusion of the drug(s) out of the microparticles and/or degradation of the polymeric particles by hydrolysis and/or enzymatic degradation. Suitable polymers include ethylcellulose and other natural or synthetic cellulose derivatives.

Polymers that are slowly soluble and form a gel in an aqueous environment, such as hydroxypropyl methylcellulose or polyethylene oxide may also be suitable as materials for drug containing microparticles. Other polymers include, but are not limited to, polyanhydrides, poly(ester anhydrides), polyhydroxy acids, such as polylactide (PLA), polyglycolide (PGA), poly(lactide-co-glycolide) (PLGA), poly-3-hydroxybutyrate (PHB) and copolymers thereof, poly-4-hydroxybutyrate (P4HB) and copolymers thereof, polycaprolactone and copolymers thereof, and combinations thereof.

Alternatively, the drug(s) can be incorporated into microparticles prepared from materials which are insoluble in aqueous solution or slowly soluble in aqueous solution, but are capable of degrading within the GI tract by means including enzymatic degradation, surfactant action of bile acids, and/or mechanical erosion. As used herein, the term “slowly soluble in water” refers to materials that are not dissolved in water within a period of 30 minutes. Preferred examples include fats, fatty substances, waxes, wax-like substances and mixtures thereof. Suitable fats and fatty substances include fatty alcohols (such as lauryl, myristyl stearyl, cetyl or cetostearyl alcohol), fatty acids and derivatives, including, but not limited to, fatty acid esters, fatty acid glycerides (mono-, di- and tri-glycerides), and hydrogenated fats. Specific examples include, but are not limited to hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated castor oil, hydrogenated oils available under the trade name Sterotex®, stearic acid, cocoa butter, and stearyl alcohol. Suitable waxes and wax-like materials include natural or synthetic waxes, hydrocarbons, and normal waxes. Specific examples of waxes include beeswax, glycowax, castor wax, carnauba wax, paraffins and candelilla wax. As used herein, a wax-like material is defined as any material that is normally solid at room temperature and has a melting point of from about 30 to 300°C.

In some cases, it may be desirable to alter the rate of water penetration into the microparticles. To this end, rate-controlling (wicking) agents may be formulated along with the fats or waxes listed above. Examples of rate-controlling materials include certain starch derivatives (e.g., waxy maltodextrin and drum dried corn starch), cellulose derivatives (e.g., hydroxypropylmethyl-cellulose, hydroxypropylcellulose, methylcellulose, and carboxymethyl-cellulose), alginic acid, lactose and talc. Additionally, a pharmaceutically acceptable surfactant (for example, lecithin) may be added to facilitate the degradation of such microparticles.

Proteins that are water insoluble, such as zein, can also be used as materials for the formation of drug containing microparticles. Additionally, proteins, polysaccharides and combinations thereof that are water soluble can

be formulated with drug into microparticles and subsequently cross-linked to form an insoluble network. For example, cyclodextrins can be complexed with individual drug molecules and subsequently cross-linked.

Encapsulation or incorporation of drug into carrier materials to produce drug containing microparticles can be achieved through known pharmaceutical formulation techniques. In the case of formulation in fats, waxes or wax-like materials, the carrier material is typically heated above its melting temperature and the drug is added to form a mixture comprising drug particles suspended in the carrier material, drug dissolved in the carrier material, or a mixture thereof. Microparticles can be subsequently formulated through several methods including, but not limited to, the processes of congealing, extrusion, spray chilling or aqueous dispersion. In a preferred process, wax is heated above its melting temperature, drug is added, and the molten wax-drug mixture is congealed under constant stirring as the mixture cools. Alternatively, the molten wax-drug mixture can be extruded and spheronized to form pellets or beads. Detailed descriptions of these processes can be found in "Remington- The science and practice of pharmacy", 20th Edition, Jennaro et. al., (Phila, Lippencott, Williams, and Wilkens, 2000).

For some carrier materials it may be desirable to use a solvent evaporation technique to produce drug containing microparticles. In this case drug and carrier material are co-dissolved in a mutual solvent and microparticles can subsequently be produced by several techniques including, but not limited to, forming an emulsion in water or other appropriate media, spray drying or by evaporating off the solvent from the bulk solution and milling the resulting material.

In some embodiments, drug in a particulate form is homogeneously dispersed in a water-insoluble or slowly water soluble material. To minimize the size of the drug particles within the composition, the drug powder itself may be milled to generate fine particles prior to formulation. The process of jet milling, known in the pharmaceutical art, can be used for this purpose. In some embodiments drug in a particulate form is homogeneously dispersed in

a wax or wax like substance by heating the wax or wax like substance above its melting point and adding the drug particles while stirring the mixture. In this case a pharmaceutically acceptable surfactant may be added to the mixture to facilitate the dispersion of the drug particles.

5 The particles can also be coated with one or more modified release coatings. Solid esters of fatty acids, which are hydrolyzed by lipases, can be spray coated onto microparticles or drug particles. Zein is an example of a naturally water-insoluble protein. It can be coated onto drug containing microparticles or drug particles by spray coating or by wet granulation
10 techniques. In addition to naturally water-insoluble materials, some substrates of digestive enzymes can be treated with cross-linking procedures, resulting in the formation of non-soluble networks. Many methods of cross-linking proteins, initiated by both chemical and physical means, have been reported. One of the most common methods to obtain cross-linking is the
15 use of chemical cross-linking agents. Examples of chemical cross-linking agents include aldehydes (gluteraldehyde and formaldehyde), epoxy compounds, carbodiimides, and genipin. In addition to these cross-linking agents, oxidized and native sugars have been used to cross-link gelatin (Cortesi, R., et al., *Biomaterials* 19 (1998) 1641-1649). Cross-linking can
20 also be accomplished using enzymatic means; for example, transglutaminase has been approved as a GRAS substance for cross-linking seafood products. Finally, cross-linking can be initiated by physical means such as thermal treatment, UV irradiation and gamma irradiation.

To produce a coating layer of cross-linked protein surrounding drug
25 containing microparticles or drug particles, a water soluble protein can be spray coated onto the microparticles and subsequently cross-linked by the one of the methods described above. Alternatively, drug containing microparticles can be microencapsulated within protein by coacervation-phase separation (for example, by the addition of salts) and subsequently
30 cross-linked. Some suitable proteins for this purpose include gelatin, albumin, casein, and gluten.

Polysaccharides can also be cross-linked to form a water-insoluble network. For many polysaccharides, this can be accomplished by reaction with calcium salts or multivalent cations that cross-link the main polymer chains. Pectin, alginate, dextran, amylose and guar gum are subject to cross-linking in the presence of multivalent cations. Complexes between oppositely charged polysaccharides can also be formed; pectin and chitosan, for example, can be complexed via electrostatic interactions.

Depot Formulations

Active agents can be formulated for depot injection. In a depot injection, the active agent is formulated with one or more pharmaceutically acceptable carriers that provide for the gradual release of active agent over a period of hours or days after injection. The depot formulation can be administered by any suitable means; however, the depot formulation is typically administered via subcutaneous or intramuscular injection.

A variety of carriers may be incorporated into the depot formulation to provide for the controlled release of the active agent. In some cases, depot formulations contain one or more biodegradable polymeric or oligomeric carriers. Suitable polymeric carriers include, but are not limited to poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid)-polyethyleneglycol (PLA-PEG) block copolymers, polyanhydrides, poly(ester anhydrides), polyglycolide (PGA), poly-3-hydroxybutyrate (PHB) and copolymers thereof, poly-4-hydroxybutyrate (P4HB), polycaprolactone, cellulose, hydroxypropyl methylcellulose, ethylcellulose, as well as blends, derivatives, copolymers, and combinations thereof.

In depot formulations containing a polymeric or oligomeric carrier, the carrier and active agent can be formulated as a solution, an emulsion, or suspension. One or more weight loss agents, and optionally one or more additional active agents, can also be incorporated into polymeric or oligomeric microparticles, nanoparticles, or combinations thereof.

In some cases, the formulation is fluid and designed to solidify or gel (*i.e.*, forming a hydrogel or organogel) upon injection. This can result from a change in solubility of the composition upon injection, or for example, by

injecting a pre-polymer mixed with an initiator and/or crosslinking agent. The polymer matrix, polymer solution, or polymeric particles entrap the active agent at the injection site. As the polymeric carrier is gradually degraded, the active agent is released, either by diffusion of the agent out of the matrix and/or dissipation of the matrix as it is absorbed. The release rate of the active agent from the injection site can be controlled by varying, for example, the chemical composition, molecular weight, crosslink density, and/or concentration of the polymeric carrier. Examples of such systems include those described in U.S. Patent Nos. 4,938,763, 5,480,656 and 6,113,943.

Depot formulations can also be prepared by using other rate-controlling excipients, including hydrophobic materials, including acceptable oils (*e.g.*, peanut oil, corn oil, sesame oil, cottonseed oil, etc.) and phospholipids, ion-exchange resins, and sparingly soluble carriers.

The depot formulation can further contain a solvent or dispersion medium containing, for example, water, ethanol, one or more polyols (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol), oils, such as vegetable oils (*e.g.*, peanut oil, corn oil, sesame oil, etc.), and combinations thereof. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

Solutions and dispersions of the weight loss agents as the free acid or base or pharmacologically acceptable salts thereof can be prepared in water or another solvent or dispersing medium suitably mixed with one or more pharmaceutically acceptable excipients including, but not limited to, surfactants, dispersants, emulsifiers, pH modifying agents, and combination thereof.

Suitable surfactants may be anionic, cationic, amphoteric or nonionic surface active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions. Examples of

anionic surfactants include sodium, potassium, ammonium of long chain alkyl sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylthioxy)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited to, quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethylbenzyl ammonium chloride, polyoxyethylene and coconut amine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate, sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, polyoxyethylene monolaurate, polysorbates, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, Poloxamer[®] 401, stearyl monoisopropanolamide, and polyoxyethylene hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl- β -alanine, sodium N-lauryl- β -iminodipropionate, myristoamphoacetate, lauryl betaine and lauryl sulfobetaine.

The formulation can contain a preservative to prevent the growth of microorganisms. Suitable preservatives include, but are not limited to, parabens, chlorobutanol, phenol, sorbic acid, and thimerosal. The formulation may also contain an antioxidant to prevent degradation of the active agent(s).

The formulation is typically buffered to a pH of 3-8 for parenteral administration upon reconstitution. Suitable buffers include, but are not limited to, phosphate buffers, acetate buffers, and citrate buffers.

Water soluble polymers are often used in formulations for parenteral administration. Suitable water-soluble polymers include, but are not limited to, polyvinylpyrrolidone, dextran, carboxymethylcellulose, and polyethylene glycol.

Sterile injectable solutions can be prepared by incorporating the active compounds in the required amount in the appropriate solvent or

dispersion medium with one or more of the excipients listed above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required
5 other ingredients from those listed above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The powders can be prepared in
10 such a manner that the particles are porous in nature, which can increase dissolution of the particles. Methods for making porous particles are well known in the art.

Implants

Implantation of a slow-release or sustained-release system, such that
15 a constant level of dosage is maintained is also contemplated herein. In such cases, the active agent(s) provided herein can be dispersed in a solid matrix optionally coated with an outer rate-controlling membrane. The compound diffuses from the solid matrix (and optionally through the outer membrane) sustained, rate-controlled release. The solid matrix and membrane may be
20 formed from any suitable material known in the art including, but not limited to, polymers, bioerodible polymers, and hydrogels.

D. Pulmonary Formulations

The compounds described herein can be formulated for parenteral administration. Pharmaceutical formulations and methods for the pulmonary
25 administration are known in the art.

The respiratory tract is the structure involved in the exchange of gases between the atmosphere and the blood stream. The respiratory tract encompasses the upper airways, including the oropharynx and larynx, followed by the lower airways, which include the trachea followed by
30 bifurcations into the bronchi and bronchioli. The upper and lower airways are called the conducting airways. The terminal bronchioli then divide into

respiratory bronchioli which then lead to the ultimate respiratory zone, the alveoli, or deep lung, where the exchange of gases occurs.

The alveolar surface area is the largest in the respiratory system and is where drug absorption occurs. The alveoli are covered by a thin
5 epithelium without cilia or a mucus blanket and secrete surfactant phospholipids. Effective delivery of therapeutic agents via pulmonary routes requires that the active agent be formulated so as to reach the alveoli.

In the case of pulmonary administration, formulations can be divided into dry powder formulations and liquid formulations. Both dry powder and
10 liquid formulations can be used to form aerosol formulations. The term aerosol as used herein refers to any preparation of a fine mist of particles, which can be in solution or a suspension, whether or not it is produced using a propellant.

Useful formulations, and methods of manufacture, are described by
15 Caryalho, et al., J Aerosol Med Pulm Drug Deliv. 2011 Apr;24(2):61-80. Epub 2011 Mar 16, for delivery of chemotherapeutic drugs to the lungs.

1. Dry Powder Formulations

Dry powder formulations are finely divided solid formulations containing one or more active agents which are suitable for pulmonary
20 administration. In dry powder formulations, the one or more active agents can be incorporated in crystalline or amorphous form.

Dry powder formulations can be administered via pulmonary inhalation to a patient without the benefit of any carrier, other than air or a suitable propellant. Preferably, however, the dry powder formulations
25 include one or more pharmaceutically acceptable carriers.

The pharmaceutical carrier may include a bulking agent, such as carbohydrates (including monosaccharides, polysaccharides, and cyclodextrins), polypeptides, amino acids, and combinations thereof. Suitable bulking agents include fructose, galactose, glucose, lactitol, lactose,
30 maltitol, maltose, mannitol, melezitose, myoinositol, palatinite, raffinose, stachyose, sucrose, trehalose, xylitol, hydrates thereof, and combinations thereof.

The pharmaceutical carrier may include a lipid or surfactant. Natural surfactants such as dipalmitoylphosphatidylcholine (DPPC) are the most preferred. This is commercially available for treatment of respiratory distress syndrome in premature infants. Synthetic and animal derived pulmonary surfactants include:

Synthetic Pulmonary Surfactants

Exosurf - a mixture of DPPC with hexadecanol and tyloxapol added as spreading agents

Pumactant (Artificial Lung Expanding Compound or ALEC) - a mixture of DPPC and PG

KL-4 - composed of DPPC, palmitoyl-oleoyl phosphatidylglycerol, and palmitic acid, combined with a 21 amino acid synthetic peptide that mimics the structural characteristics of SP-B.

Venticute - DPPC, PG, palmitic acid and recombinant SP-C

Animal derived surfactants

Alveofact - extracted from cow lung lavage fluid

Curosurf - extracted from material derived from minced pig lung

Infasurf - extracted from calf lung lavage fluid

Survanta - extracted from minced cow lung with additional DPPC, palmitic acid and tripalmitin

Exosurf, Curosurf, Infasurf, and Survanta are the surfactants currently FDA approved for use in the U.S.

The pharmaceutical carrier may also include one or more stabilizing agents or dispersing agents. The pharmaceutical carrier may also include one or more pH adjusters or buffers. Suitable buffers include organic salts prepared from organic acids and bases, such as sodium citrate or sodium ascorbate. The pharmaceutical carrier may also include one or more salts, such as sodium chloride or potassium chloride.

Dry powder formulations are typically prepared by blending one or more active agents with a pharmaceutical carrier. Optionally, additional active agents may be incorporated into the mixture. The mixture is then formed into particles suitable for pulmonary administration using techniques

known in the art, such as lyophilization, spray drying, agglomeration, spray coating, extrusion processes, hot melt particle formation, phase separation particle formation (spontaneous emulsion particle formation, solvent evaporation particle formation, and solvent removal particle formation),
5 coacervation, low temperature casting, grinding, milling (*e.g.*, air-attrition milling (jet milling), ball milling), high pressure homogenization, and/or supercritical fluid crystallization.

An appropriate method of particle formation can be selected based on the desired particle size, particle size distribution, and particle morphology.
10 In some cases, the method of particle formation is selected so as to produce a population of particles with the desired particle size, particle size distribution for pulmonary administration. Alternatively, the method of particle formation can produce a population of particles from which a population of particles with the desired particle size, particle size distribution for
15 pulmonary administration is isolated, for example by sieving.

It is known in the art that particle morphology affects the depth of penetration of a particle into the lung as well as uptake of the drug particles. As discussed above, drug particles should reach the alveoli to maximize therapeutic efficacy. Accordingly, dry powder formulations is processed
20 into particles having the appropriate mass median aerodynamic diameter (MMAD), tap density, and surface roughness to achieve delivery of the one or more active agents to the deep lung. Preferred particle morphologies for delivery to the deep lung are known in the art, and are described, for example, in U.S. Patent No. 7,052,678 to Vanbever, *et al.*

25 Particles having a mass median aerodynamic diameter (MMAD) of greater than about 5 microns generally do not reach the lung; instead, they tend to impact the back of the throat and are swallowed. Particles having diameters of about 3 to about 5 microns are small enough to reach the upper- to mid-pulmonary region (conducting airways), but may be too large to reach
30 the alveoli. Smaller particles, (*i.e.*, about 0.5 to about 3 microns), are capable of efficiently reaching the alveolar region. Particles having diameters smaller than about 0.5 microns can also be deposited in the

alveolar region by sedimentation, although very small particles may be exhaled.

The precise particle size range effective to achieve delivery to the alveolar region will depend on several factors, including the tap density of particles being delivered. Generally speaking, as tap density decreases, the
5 MMAD of particles capable of efficiently reaching the alveolar region of the lungs increases. Therefore, in cases of particles with low tap densities, particles having diameters of about 3 to about 5 microns, about 5 to about 7 microns, or about 7 to about 9.5 microns can be efficiently delivered to the
10 lungs. The preferred aerodynamic diameter for maximum deposition within the lungs can be calculated. See, for example, U.S. Patent No. 7,052,678 to Vanbever, *et al.*

In some embodiments, the dry powder formulation is composed of a plurality of particles having a median mass aerodynamic diameter between
15 about 0.5 to about 10 microns, more preferably between about 0.5 microns to about 7 microns, most preferably between about 0.5 to about 5 microns. In some embodiments, the dry powder formulation is composed of a plurality of particles having a median mass aerodynamic diameter between about 0.5 to about 3 microns. In some embodiments, the dry powder formulation is
20 composed of a plurality of particles having a median mass aerodynamic diameter between about 3 to about 5 microns. In some embodiments, the dry powder formulation is composed of a plurality of particles having a median mass aerodynamic diameter between about 5 to about 7 microns. In some embodiments, the dry powder formulation is composed of a plurality of
25 particles having a median mass aerodynamic diameter between about 7 to about 9.5 microns.

In some cases, there may be an advantage to delivering particles larger than about 3 microns in diameter. Phagocytosis of particles by alveolar macrophages diminishes precipitously as particle diameter increases
30 beyond about 3 microns. Kawaguchi, H., *et al.*, *Biomaterials* 7: 61-66 (1986); and Rudt, S. and Muller, R. H., *J. Contr. Rel*, 22: 263-272 (1992). By administering particles with an aerodynamic volume greater than 3

microns, phagocytic engulfment by alveolar macrophages and clearance from the lungs can be minimized.

In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least about 95% of the particles in dry powder
5 formulation have aerodynamic diameter of less than about 10 microns, more preferably less than about 7 microns, most preferably about 5 microns. In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least about 95%, of the particles in dry powder
10 formulation have aerodynamic diameter of greater than about 0.5 microns. In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least about 95%, of the particles in dry powder
15 formulation have an aerodynamic diameter of greater than about 0.1 microns.

In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least about 95%, of the particles in dry
15 powder formulation have aerodynamic diameter of greater than about 0.5 microns and less than about 10 microns, more preferably greater than about 0.5 microns and less than about 7 microns, most preferably greater than about 0.5 microns and less than about 5 microns. In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least
20 about 95% of the particles in dry powder formulation have aerodynamic diameter of greater than about 0.5 microns and less than about 3 microns. In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least about 95% of the particles in dry powder formulation
25 have aerodynamic diameter of greater than about 3 microns and less than about 5 microns. In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least about 95% of the particles in dry powder formulation have aerodynamic diameter of greater than about 5 microns and less than about 7 microns. In some embodiments, at least about 80%, more preferably at least about 90%, most preferably at least about 95%
30 of the particles in dry powder formulation have aerodynamic diameter of greater than about 7 microns and less than about 9.5 microns.

In some embodiments, the particles have a tap density of less than about 0.4 g/cm^3 , more preferably less than about 0.25 g/cm^3 , most preferably less than about 0.1 g/cm^3 . Features which can contribute to low tap density include irregular surface texture and porous structure.

5 In some cases, the particles are spherical or ovoid in shape. The particles can have a smooth or rough surface texture. The particles may also be coated with a polymer or other suitable material to control release of one or more active agents in the lungs.

10 Dry powder formulations can be administered as dry powder using suitable methods known in the art. Alternatively, the dry powder formulations can be suspended in the liquid formulations described below, and administered to the lung using methods known in the art for the delivery of liquid formulations.

2. *Liquid Formulations*

15 Liquid formulations contain one or more weight loss agents dissolved or suspended in a liquid pharmaceutical carrier.

Suitable liquid carriers include, but are not limited to distilled water, de-ionized water, pure or ultrapure water, saline, and other physiologically acceptable aqueous solutions containing salts and/or buffers, such as
20 phosphate buffered saline (PBS), Ringer's solution, and isotonic sodium chloride, or any other aqueous solution acceptable for administration to an animal or human.

Preferably, liquid formulations are isotonic relative to physiological fluids and of approximately the same pH, ranging e.g., from about pH 4.0 to
25 about pH 7.4, more preferably from about pH 6.0 to pH 7.0. The liquid pharmaceutical carrier can include one or more physiologically compatible buffers, such as a phosphate buffers. One skilled in the art can readily determine a suitable saline content and pH for an aqueous solution for pulmonary administration.

30 Liquid formulations may include one or more suspending agents, such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone, gum

tragacanth, or lecithin. Liquid formulations may also include one or more preservatives, such as ethyl or *n*-propyl *p*-hydroxybenzoate.

In some cases the liquid formulation may contain one or more solvents that are low toxicity organic (*i.e.*, nonaqueous) class 3 residual
5 solvents, such as ethanol, acetone, ethyl acetate, tetrahydrofuran, ethyl ether, and propanol. These solvents can be selected based on their ability to readily aerosolize the formulation. Any such solvent included in the liquid
10 formulation should not detrimentally react with the one or more active agents present in the liquid formulation. The solvent should be sufficiently volatile to enable formation of an aerosol of the solution or suspension. Additional
solvents or aerosolizing agents, such as a freon, alcohol, glycol, polyglycol, or fatty acid, can also be included in the liquid formulation as desired to
increase the volatility and/or alter the aerosolizing behavior of the solution or
suspension.

15 Liquid formulations may also contain minor amounts of polymers, surfactants, or other excipients well known to those of the art. In this context, "minor amounts" means no excipients are present that might adversely affect uptake of the one or more active agents in the lungs.

3. *Aerosol Formulations*

The dry powder and liquid formulations described above can be used to form aerosol formulations for pulmonary administration. Aerosols for the delivery of therapeutic agents to the respiratory tract are known in the art.

5 The term aerosol as used herein refers to any preparation of a fine mist of solid or liquid particles suspended in a gas. In some cases, the gas may be a propellant; however, this is not required. Aerosols may be produced using a number of standard techniques, including as ultrasonication or high pressure treatment.

10 Preferably, a dry powder or liquid formulation as described above is formulated into aerosol formulations using one or more propellants. Suitable propellants include air, hydrocarbons, such as pentane, isopentane, butane, isobutane, propane and ethane, carbon dioxide, chlorofluorocarbons, fluorocarbons, and combinations thereof. Suitable fluorocarbons include 1-6
15 hydrogen containing fluorocarbons, such as CHF_2CHF_2 , $\text{CF}_3\text{CH}_2\text{F}$, $\text{CH}_2\text{F}_2\text{CH}_3$, and $\text{CF}_3\text{CHF}_2\text{CF}_3$ as well as fluorinated ethers such as $\text{CF}_3\text{-O-}$
 CF_3 , $\text{CF}_2\text{H-O-CHF}_2$, and $\text{CF}_3\text{-CF}_2\text{-O-CF}_2\text{-CH}_3$. Suitable fluorocarbons also include perfluorocarbons, such as 1-4 carbon perfluorocarbons including CF_3CF_3 , $\text{CF}_3\text{CF}_2\text{CF}_3$, and $\text{CF}_3\text{CF}_2\text{CF}_2\text{CF}_3$.

20 Preferably, the propellants include, but not limited to, one or more hydrofluoroalkanes (HFA). Suitable HFA propellants, include but are not limited to, 1,1,1,2,3,3,-heptafluoro-n-propane (HFA 227), 1,1,1,2-
tetrafluoroethane (HFA 134) 1,1,1,2, 25 3,3,3-heptafluoropropane (Propellant 227), or any mixture of these propellants.

25 Preferably, the one or more propellants have sufficient vapor pressure to render them effective as propellants. Preferably, the one or more propellants are selected so that the density of the mixture is matched to the density of the particles in the aerosol formulation in order to minimize settling or creaming of the particles in the aerosol formulation.

30 The propellant is preferably present in an amount sufficient to propel a plurality of the selected doses of the aerosol formulation from an aerosol canister.

4. *Devices for Pulmonary Administration*

In some cases, a device is used to administer the formulations to the lungs. Suitable devices include, but are not limited to, dry powder inhalers, pressurized metered dose inhalers, nebulizers, and electrohydrodynamic
5 aerosol devices.

Inhalation can occur through the nose and/or the mouth of the patient. Administration can occur by self-administration of the formulation while inhaling, or by administration of the formulation via a respirator to a patient on a respirator.

10 *Dry Powder Inhalers*

The dry powder formulations described above can be administered to the lungs of a patient using a dry powder inhaler (DPI). DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which can then be inhaled by the patient.

15 In a dry powder inhaler, the dose to be administered is stored in the form of a non-pressurized dry powder and, on actuation of the inhaler, the particles of the powder are inhaled by the subject. In some cases, a compressed gas (*i.e.*, propellant) may be used to dispense the powder, similar to pressurized metered dose inhalers (pMDIs). In some cases, the DPI may
20 be breath-actuated, meaning that an aerosol is created in precise response to inspiration. Typically, dry powder inhalers administer a dose of less than a few tens of milligrams per inhalation to avoid provocation of cough.

DPIs function via a variety of mechanical means to administer formulations to the lungs. In some DPIs, a doctor blade or shutter slides
25 across the dry powder formulation contained in a reservoir, culling the formulation into a flowpath whereby the patient can inhale the powder in a single breath. In other DPIs, the dry powder formulation is packaged in a preformed dosage form, such as a blister, tabule, tablet, or gelcap, which is pierced, crushed, or otherwise unsealed to release the dry powder
30 formulation into a flowpath for subsequent inhalation. Still others DPIs release the dry powder formulation into a chamber or capsule and use

mechanical or electrical agitators to keep the dry powder formulation suspended in the air until the patient inhales.

Dry powder formulations may be packaged in various forms, such as a loose powder, cake, or pressed shape for insertion in to the reservoir of a
5 DPI.

Examples suitable DPIs for the administration of the formulations described above include the Turbohaler® inhaler (Astrazeneca, Wilmington, Del.), the Clickhaler® inhaler (Innovata, Ruddington, Nottingham, UK), the Diskus® inhaler (Glaxo, Greenford, Middlesex, UK), the EasyHaler®
10 (Orion, Espoo, FI), the Exubera® inhaler (Pfizer, New York, N.Y.), the Qdose® inhaler (Microdose, Monmouth Junction, N.J.), and the Spiros® inhaler (Dura, San Diego, Calif.).

Pressurized Metered Dose Inhalers

The liquid formulations described above can be administered to the
15 lungs of a patient using a pressurized metered dose inhaler (pMDI).

Pressurized Metered Dose Inhalers (pMDIs) generally include at least two components: a canister in which the liquid formulation is held under pressure in combination with one or more propellants, and a receptacle used to hold and actuate the canister. The canister may contain a single or
20 multiple doses of the formulation. The canister may include a valve, typically a metering valve, from which the contents of the canister may be discharged. Aerosolized drug is dispensed from the pMDI by applying a force on the canister to push it into the receptacle, thereby opening the valve and causing the drug particles to be conveyed from the valve through the
25 receptacle outlet. Upon discharge from the canister, the liquid formulation is atomized, forming an aerosol.

pMDIs typically employ one or more propellants to pressurize the contents of the canister and to propel the liquid formulation out of the receptacle outlet, forming an aerosol. Any suitable propellants, including
30 those discussed above, may be utilized. The propellant may take a variety of forms. For example, the propellant may be a compressed gas or a liquefied gas. Chlorofluorocarbons (CFC) were once commonly used as liquid

propellants, but have now been banned. They have been replaced by the now widely accepted hydrofluororalkane (HFA) propellants.

pMDIs are available from a number of suppliers, including 3M Corporation, Aventis, Boehringer Ingelheim, Forest Laboratories, Glaxo-
5 Wellcome, Schering Plough and Vectura. In some cases, the patient administers an aerosolized formulation by manually discharging the aerosolized formulation from the pMDI in coordination with inspiration. In this way, the aerosolized formulation is entrained within the inspiratory air flow and conveyed to the lungs.

10 In other cases, a breath-actuated trigger, such as that included in the Tempo® inhaler (MAP Pharmaceuticals, Mountain View, Calif.) may be employed that simultaneously discharges a dose of the formulation upon sensing inhalation. These devices, which discharge the aerosol formulation when the user begins to inhale, are known as breath-actuated pressurized
15 metered dose inhalers (baMDIs).

Nebulizers

The liquid formulations described above can also be administered using a nebulizer. Nebulizers are liquid aerosol generators that convert the liquid formulation described above, usually aqueous-based compositions, into
20 mists or clouds of small droplets, preferably having diameters less than 5 microns mass median aerodynamic diameter, which can be inhaled into the lower respiratory tract. This process is called atomization. The droplets carry the one or more active agents into the nose, upper airways or deep lungs when the aerosol cloud is inhaled. Any type of nebulizer may be used
25 to administer the formulation to a patient, including, but not limited to pneumatic (jet) nebulizers and electromechanical nebulizers.

Pneumatic (jet) nebulizers use a pressurized gas supply as a driving force for atomization of the liquid formulation. Compressed gas is delivered through a nozzle or jet to create a low pressure field which entrains a
30 surrounding liquid formulation and shears it into a thin film or filaments. The film or filaments are unstable and break up into small droplets that are carried by the compressed gas flow into the inspiratory breath. Baffles

inserted into the droplet plume screen out the larger droplets and return them to the bulk liquid reservoir. Examples of pneumatic nebulizers include, but are not limited to, PARI LC Plus®, PARI LC Sprint®, Devilbiss PulmoAide®, and Boehringer Ingelheim Respima®.

5 Electromechanical nebulizers use electrically generated mechanical force to atomize liquid formulations. The electromechanical driving force can be applied, for example, by vibrating the liquid formulation at ultrasonic frequencies, or by forcing the bulk liquid through small holes in a thin film. The forces generate thin liquid films or filament streams which break up into
10 small droplets to form a slow moving aerosol stream which can be entrained in an inspiratory flow.

 In some cases, the electromechanical nebulizer is an ultrasonic nebulizer, in which the liquid formulation is coupled to a vibrator oscillating at frequencies in the ultrasonic range. The coupling is achieved by placing
15 the liquid in direct contact with the vibrator such as a plate or ring in a holding cup, or by placing large droplets on a solid vibrating projector (a horn). The vibrations generate circular standing films which break up into droplets at their edges to atomize the liquid formulation. Examples of ultrasonic nebulizers include DuroMist®, Drive Medical Beetle Neb®,
20 Octive Tech Densylogic®, and John Bunn Nano-Sonic®.

 In some cases, the electromechanical nebulizer is a mesh nebulizer, in which the liquid formulation is driven through a mesh or membrane with small holes ranging from 2 to 8 microns in diameter, to generate thin filaments which break up into small droplets. In certain designs, the liquid
25 formulation is forced through the mesh by applying pressure with a solenoid piston driver (for example, the AERx® nebulizer), or by sandwiching the liquid between a piezoelectrically vibrated plate and the mesh, which results in a oscillatory pumping action (for example EFlow®, AerovectRx®, or TouchSpray® nebulizer). In other cases, the mesh vibrates back and forth
30 through a standing column of the liquid to pump it through the holes. Examples of such nebulizers include the AeroNeb Go®, AeroNeb Pro®, PARI EFlow®, Omron 22UE®; and Aradigm AERx®.

Electrohydrodynamic Aerosol Devices

The liquid formulations described above can also be administered using an electrohydrodynamic (EHD) aerosol device. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions.

5 Examples of EHD aerosol devices are known in the art. See, for example, U.S. Patent No. 4,765,539 to Noakes *et al.* and U.S. Patent No. 4,962,885 to Coffee, R.A.

The electrochemical properties of the formulation may be important parameters to optimize when delivering the liquid formulation to the lung
10 with an EHD aerosol device and such optimization is routinely performed by one of skill in the art.

IV. Methods of treatment

Pharmaceutical formulations containing one or more of the weight loss agents described herein can be administered to induce weight loss in a
15 pre-obese, obese, or morbidly obese patient, reduce body fat in a pre-obese, obese, or morbidly obese patient, reduce food intake in a pre-obese, obese, or morbidly obese patient, improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient, prevent weight gain and/or prevent an increase in body mass index in a normal, pre-obese, obese, or morbidly obese patient, or
20 combinations thereof.

In certain embodiments, the pharmaceutical formulations are administered to a patient suffering from obesity (*e.g.*, a pre-obese, obese, or morbidly obese patient), an obesity-related disease or disorder, diabetes, insulin-resistance syndrome, lipodystrophy, nonalcoholic steatohepatitis, a
25 cardiovascular disease, polycystic ovary syndrome, or a metabolic syndrome.

In cases where the pharmaceutical formulations are administered to normalize blood sugar, the formulations are preferably administered in an amount effective to lower blood glucose levels to less than about 180 mg/dL. The formulations can be co-administered with other anti-diabetic therapies, if
30 necessary, to improve glucose homeostasis.

Pharmaceutical formulations may also be administered to patients suffering from a disease or disorder that causes obesity or predisposes a

patient to become obese, such as Bardet-Biedl syndrome or a mutation in the gene encoding for the melanocortin receptor 3 (MC3R) protein (*i.e.*, an MC3R mutation).

A. Dosages

5 The precise dosage administered to a patient will depend on many factors, including the physical characteristics of the patient (*e.g.*, weight), the degree of severity of the disease or disorder to be treated, and the presence or absence of other complicating diseases or disorders and can be readily determined by the prescribing physician.

10 In certain embodiments, the weight loss agent is administered at a dosage equivalent to an oral dosage of between about 0.005 mg and about 500 mg per kg of body weight per day, more preferably between about 0.05 mg and about 100 mg per kg of body weight per day, most preferably between about 0.1 mg and about 10 mg per kg of body weight per day. In particular embodiments, the weight loss agent is administered at a dosage
15 equivalent to an oral dosage of between about 1.0 mg and 15.0 mg per kg of body weight per day, preferably about 5.0 mg to about 15.0 mg per kg of body weight. In some embodiments, the dosage is about 10 mg per kg of body weight.

20 In some cases, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to induce weight loss. In certain embodiments, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly
25 obese patient in a therapeutically effective amount to decrease body mass by at least 10%, more preferably by at least 15%, most preferably by at least 20%.

 In some cases, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly
30 obese patient in a therapeutically effective amount to reduce body fat. In certain embodiments, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly

obese patient in a therapeutically effective amount to decrease body fat by at least 10%, more preferably by at least 15%, most preferably by at least 20%.

In some cases, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to reduce food intake, appetite, or combinations thereof. In certain embodiments, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to reduce average daily food intake (in terms of calories) by at least 15%, more preferably by at least 25%, most preferably by at least 35%.

In some cases, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to improve glucose homeostasis. In certain embodiments, a pharmaceutical formulation containing one or more of the weight loss agents is administered to a pre-obese, obese, or morbidly obese patient in a therapeutically effective amount to reduce average fasting plasma blood glucose by at least 10%, more preferably by at least 15%, most preferably by at least 20%. In cases where the pharmaceutical formulations are administered to normalize blood sugar, the formulations are preferably administered in an amount effective to lower overnight fasted plasma glucose levels to less than about 180 mg/dL, 160 mg/dL, 140 mg/dL, 120 mg/dL, or 100 mg/dL.

B. Therapeutic Administration

Pharmaceutical formulations may be administered, for example, in a single dosage, as a continuous dosage, one or more times daily, or less frequently, such as once a week. The pharmaceutical formulations can be administered once a day or more than once a day, such as twice a day, three times a day, four times a day or more. In certain embodiments, the formulations are administered orally, once daily or less.

The pharmaceutical formulations are administered in an effective amount and for an effective period of time to elicit the desired therapeutic benefit. In certain embodiments, the pharmaceutical formulation is

administered daily, bi-weekly, weekly, bi-monthly or monthly for a period of at least one week, two weeks, three weeks, four weeks, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, or longer.

5 The pharmaceutical formulations may also be administered prophylactically, *e.g.*, to patients or subjects who are at risk for a disease or disorder such as diabetes or obesity. Thus, methods can also involve identifying a subject at risk for diabetes or obesity prior to administration of the formulations.

10 The exact amount of the formulations required will vary from subject to subject, depending on the species, age, sex, weight and general condition of the subject, extent of the disease in the subject, route of administration, whether other drugs are included in the regimen, and the like. Thus, it is not possible to specify an exact dosages for every formulation. However, an
15 appropriate dosage can be determined by one of ordinary skill in the art using only routine experimentation. For example, effective dosages and schedules for administering the compositions may be determined empirically, and making such determinations is within the skill in the art.

Dosage can vary, and can be administered in one or more dose
20 administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products.

Administration of gambogic acid (SR-03, 0.5 mg/kg), tanespimycin (AAG, 15 mg/kg), and NVP-AUY922 (15 mg/kg) significantly decreased the
25 body weight of mice fed a high fat diet (HFD) while little or no decrease was observed in lean mice. The data for SR-03 also show a significant decrease in food intake for HFD mice with little or no effect on food intake in lean mice and that the effect is mediated through leptin signaling.

1. Co-Administration with Active Agents

30 In other embodiments, the compounds disclosed herein can be co-administered with one or more additional therapeutic, prophylactic, or diagnostic agents. Co-administration, as used herein, includes administration

within the same dosage form or within different dosage forms. For those
embodiments where the compounds described herein and the one or more
additional therapeutic, prophylactic, or diagnostic agents are administered in
different dosage forms, the dosage forms can be administered simultaneously
5 (e.g., at the same time or essentially at the same time) or sequentially.
“Essentially at the same time” as used herein generally means within ten
minutes, preferably within five minutes, more preferably within two minutes,
most preferably within in one minute. Dosage forms administered
sequentially can be administered within several hours of each other, e.g.,
10 with ten hours, nine hours, eight hours, seven hours, six hours, five hours,
four hours, three hours, two hours, one hour, 30 minutes, 20 minutes, or 15
minutes.

In certain embodiments, the weight loss agents described herein are
co-administered with leptin or a leptin analog. In these cases, leptin or a
15 leptin analog may be co-administered with the weight loss agents for a
portion of the treatment period, or during the entirety of the treatment period.
In preferred embodiments, the weight loss agents are co-administered with r-
metHuLeptin (A-100, METRELEPTIN®), available from Amylin
Pharmaceuticals (San Diego, Calif.).

20 In certain embodiments, the patients are suffering from diabetes. In
these cases, the weight loss agents described herein may be co-administered
with one or more therapies for diabetes.

Examples

Example 1. Administration of gambogic acid to obese mice

25 To investigate whether gambogic acid can act as an anti-obesity drug
by increasing leptin sensitivity and reducing appetite, C57Bl/6J mice were
placed on a high fat diet (HFD; Research Diets, D12451, 45 kcal% fat)
feeding for 16 weeks. After establishment of obesity and leptin resistance,
mice were administered gambogic acid (at 0.5 mg/kg, in 25 µl DMSO, once
30 per day) and vehicle (DMSO, 25 µl) with intraperitoneal (i.p.) injection. The
animals had free access to food and water unless otherwise stated. In all
experiments, three days prior to drug administration, the animals went

through an acclimation period where they were given DMSO (25 μ l) to reduce the effect of stress created by i.p. injection.

Following three days acclimation, mice were administered gambogic acid daily i.p. injections at 0.5 mg/kg for three weeks in 25 μ l of DMSO as vehicle, whereas the control group received the same volume of DMSO. I.p. administration of gambogic acid significantly decreased the body weight of HFD-fed obese (Figure 1A) and food intake (Figure 1B).

Gambogic acid was administered to 10-week old lean mice on chow diet at 0.5 mg/kg for three weeks by i.p. injections. As shown in Figures 1C and 1D, gambogic acid failed to induce bodyweight loss or food intake in lean mice, suggesting that the anorectic effect of gambogic acid is limited to obese animals.

To explore whether gambogic acid's effect is leptin dependent, gambogic acid (0.5 mg/kg, once a day, in 25 μ l DMSO) was administered to leptin receptor deficient (*db/db*) mice. The body weight and food intake of *db/db* mice continued to increase similar to the vehicle treated group (Figures 1E and 1F).

The fact that gambogic acid decreased body weight in HFD-fed obese mice but not in *db/db* mice suggests that anorectic effect of gambogic is mediated through leptin signaling. Although HFD-fed obese mice have elevated leptin levels, they develop leptin resistance and do not respond to exogenous leptin administration. Therefore is it possible that gambogic acid exerts the anti-obesity effects through increasing the leptin sensitivity in the brains of the HFD-fed obese mice.

25 **Example 2. Administration of tanespimycin to obese mice**

To investigate whether tanespimycin can act as an anti-obesity drug by increasing leptin sensitivity and reducing appetite, C57Bl/6J mice were placed on a high fat diet (HFD; Research Diets, D12451, 45 kcal% fat) feeding for 16 weeks. After establishment of obesity and leptin resistance, mice were administered tanespimycin (at 15 mg/kg, in 25 μ l DMSO, once per day) and vehicle (DMSO, 25 μ l) with intraperitoneal (i.p.) injection. The animals had free access to food and water unless otherwise stated. In all

experiments, three days prior to drug administration, the animals went through an acclimation period where they were given DMSO (25 μ l) to reduce the effect of stress created by i.p. injection.

Following three days acclimation, mice were administered
5 tanespimycin daily i.p. injections at 15 mg/kg for three weeks in 25 μ l of DMSO as vehicle, whereas the control group received the same volume of DMSO. I.p. administration of tanespimycin significantly decreased the body weight of HFD-fed obese (Figure 2A).

Tanespimycin was administered to 10-week old lean mice on chow
10 diet at 15 mg/kg for three weeks by i.p. injections. As shown in Figure 2B, tanespimycin failed to induce bodyweight loss or food intake in lean mice, suggesting that the anorectic effect of tanespimycin is limited to obese animals.

Example 3. Administration of NVP-AUY922 to obese mice

15 To investigate whether NVP-AUY922 can act as an anti-obesity drug by increasing leptin sensitivity and reducing appetite, C57Bl/6J mice were placed on a high fat diet (HFD; Research Diets, D12451, 45 kcal% fat) feeding for 16 weeks. After establishment of obesity and leptin resistance, mice were administered NVP-AUY922 (at 15 mg/kg, in 25 μ l DMSO, once
20 per day) and vehicle (DMSO, 25 μ l) with intraperitoneal (i.p.) injection. The animals had free access to food and water unless otherwise stated. In all experiments, three days prior to drug administration, the animals went through an acclimation period where they were given DMSO (25 μ l) to reduce the effect of stress created by i.p. injection.

25 Following three days acclimation, mice were administered NVP-AUY922 daily i.p. injections at 15 mg/kg for three weeks in 25 μ l of DMSO as vehicle, whereas the control group received the same volume of DMSO. I.p. administration of NVP-AUY922 significantly decreased the body weight of HFD-fed obese (Figure 3A).

30 NVP-AUY922 was administered to 10-week old lean mice on chow diet at 15 mg/kg for three weeks by i.p. injections. As shown in Figure 3B, NVP-AUY922 failed to induce bodyweight loss or food intake in lean mice,

suggesting that the anorectic effect of NVP-AUY922 is limited to obese animals.

We claim:

1. A pharmaceutical composition comprising an HSP90 inhibitor in a therapeutically effective amount to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient; or combinations thereof.

2. The composition of claim 1, wherein the HSP90 inhibitor is selected from the group consisting of xanthonoids; benzoquinone ansamycin antibiotics; resorcinol derivatives; purine analogs; other compounds, such as SNX-5422, DS-2248, and XL-888; and combinations thereof.

3. The composition of claim 2, wherein the xanthoid is selected from the group consisting of gambogic acid and derivatives thereof.

4. The composition of claim 2, wherein the benzoquinone ansamycin antibiotics are selected from the group consisting of geldanamycin and derivatives thereof.

5. The composition of claim 4, wherein the geldanamycin derivatives are selected from the group consisting of tanespimycin, alvespimycin, retaspimycin, and IPI-493.

6. The composition of claim 2, wherein the resorcinol derivatives are selected from the group consisting of ganetespib, NVP-AUY922, AT-13387, and KW-2478.

7. The composition of claim 2, wherein the purine analogs are selected from the group consisting of BIIB021 (CNF 2024), MPC-3100, Debio 0932 (CUDC-305), and PU-H71.

8. The composition of claim 3, wherein the inhibitor is gambogic acid.

9. The composition of claim 5, wherein the inhibitor is tanespimycin.

10. The composition of claim 6, wherein the inhibitor is NVP-AUY922.

11. The composition of any one of claims 1-10, further comprising leptin, a leptin analog, or combinations thereof.

12. A method of inducing weight loss in a pre-obese, obese, or morbidly obese patient, comprising administering a pharmaceutical composition defined by any one of claims 1-11.

13. The method of claim 12, wherein the pharmaceutical composition is administered in an effective amount to decrease body mass by at least 10%, more preferably by at least 15%, most preferably by at least 20%.

14. A method of reducing body fat in a pre-obese, obese, or morbidly obese patient, comprising administering a pharmaceutical composition defined by any one of claims 1-11.

15. The method of claim 14, wherein the pharmaceutical composition is administered in an effective amount to decrease body fat by at least 10%, more preferably by at least 15%, most preferably by at least 20%.

16. A method of reducing food intake in a pre-obese, obese, or morbidly obese patient, comprising administering a pharmaceutical composition defined by any one of claims 1-11.

17. The method of claim 16, wherein the pharmaceutical composition is administered in an effective amount to reduce average daily food intake (in terms of calories) by at least 15%, more preferably by at least 25%, most preferably by at least 35%.

18. A method of improving glucose homeostasis in a pre-obese, obese, or morbidly obese patient, comprising administering a pharmaceutical composition defined by any one of claims 1-11.

19. The method of claim 18, wherein the pharmaceutical composition is administered in an effective amount to reduce average fasting plasma blood glucose by at least 10%, more preferably by at least 15%, most preferably by at least 20%.

20. The method of claim 18, wherein the pharmaceutical composition is preferably administered in an amount effective to lower blood glucose levels to less than about 180 mg/dL.

21. The method of claim 18, wherein the composition further comprises one or more anti-diabetic agents to improve glucose homeostasis.

22. A method of preventing an increase in the body mass index of a normal, pre-obese, obese, or morbidly obese patient, comprising administering a pharmaceutical composition defined by any one of claims 1-11.

23. The method of any one of claims 12-22, further comprising co-administering leptin, a leptin analog, or combinations thereof.

24. The method of any one of claims 12-23, wherein the composition is administered enterally or parenterally.

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HFD WT

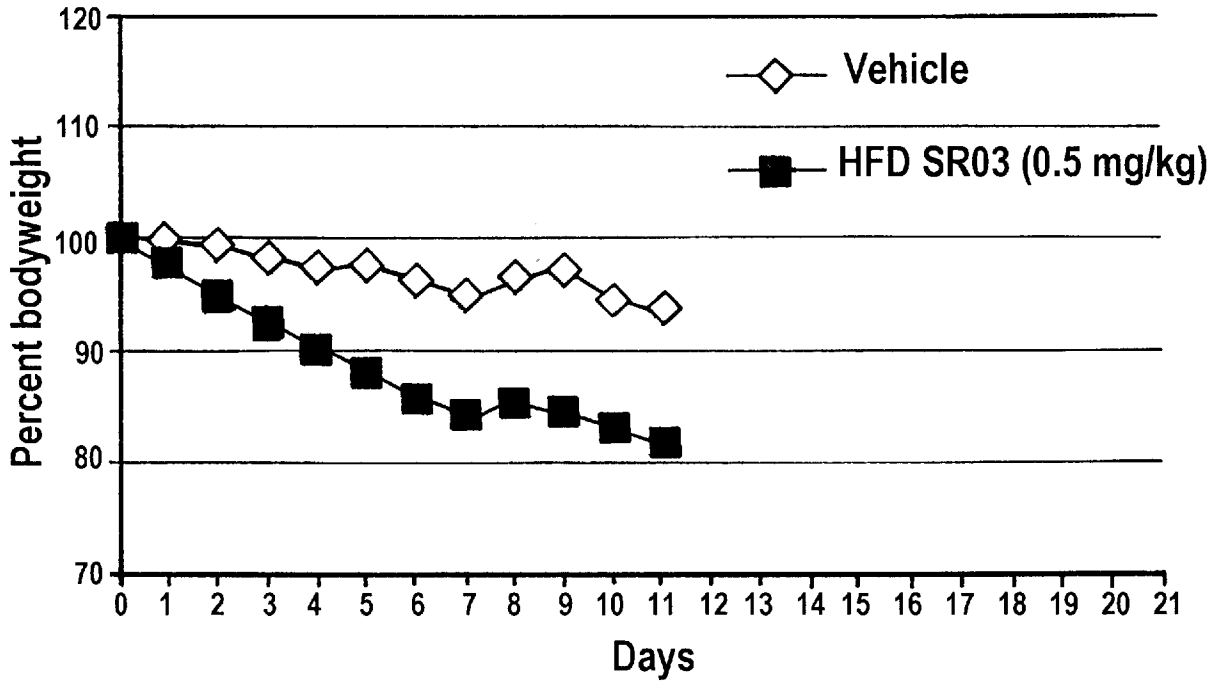


FIG. 1A

HFD WT

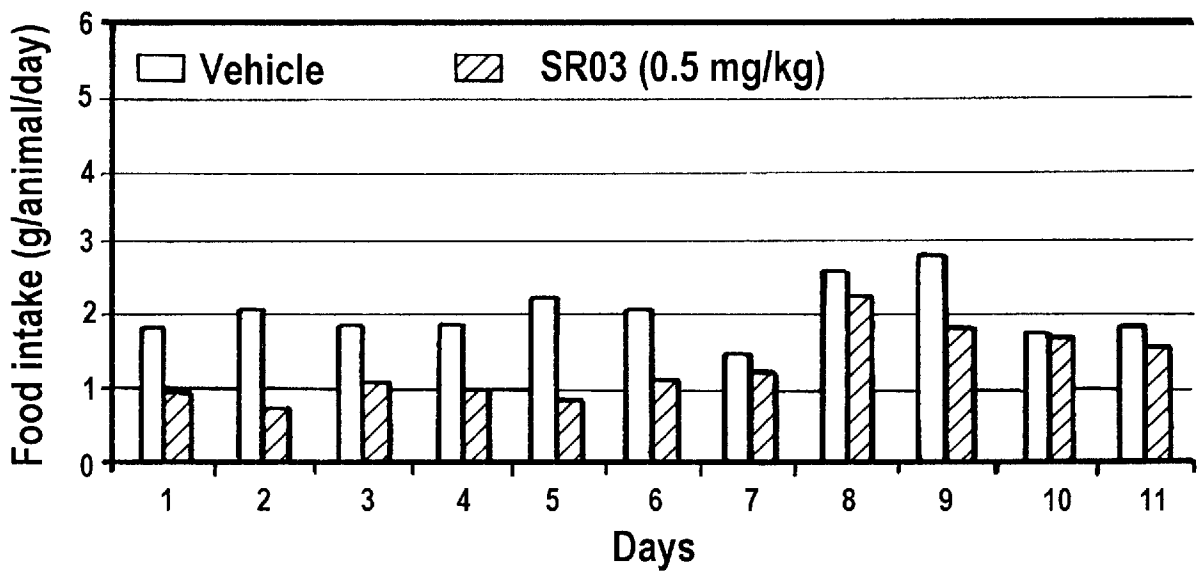
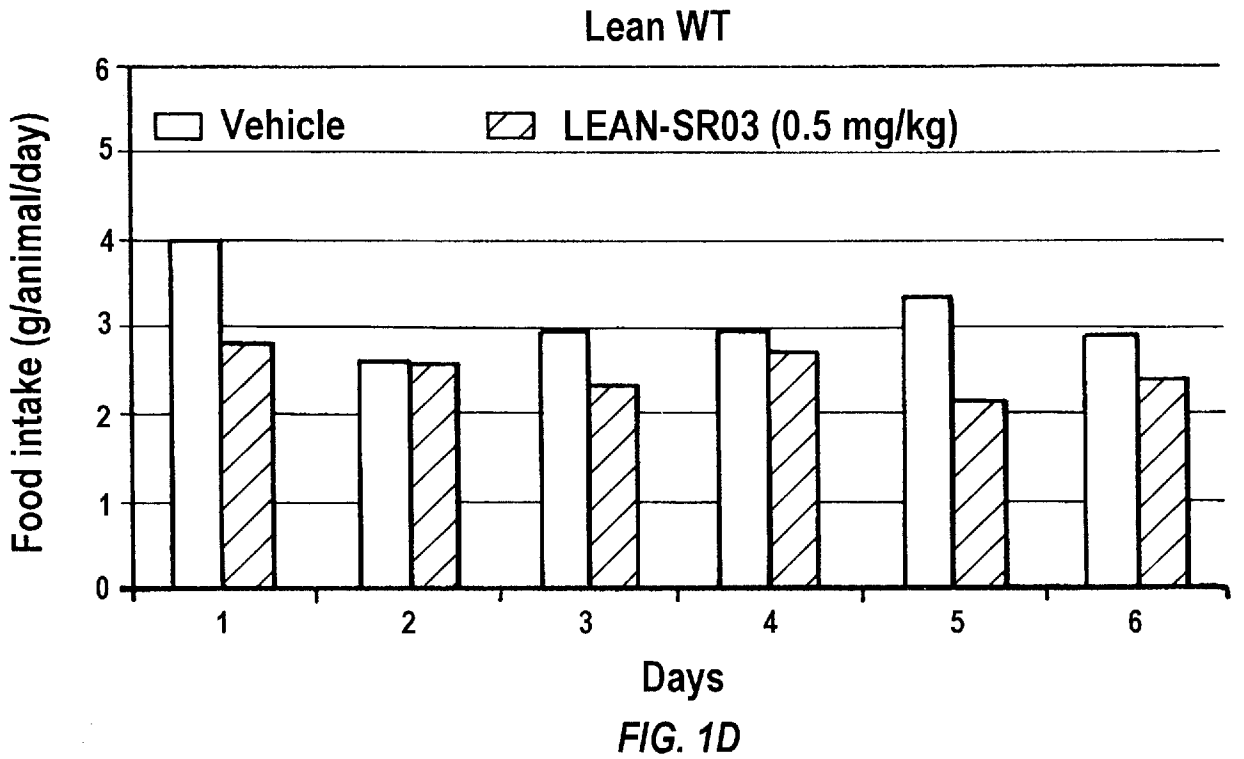
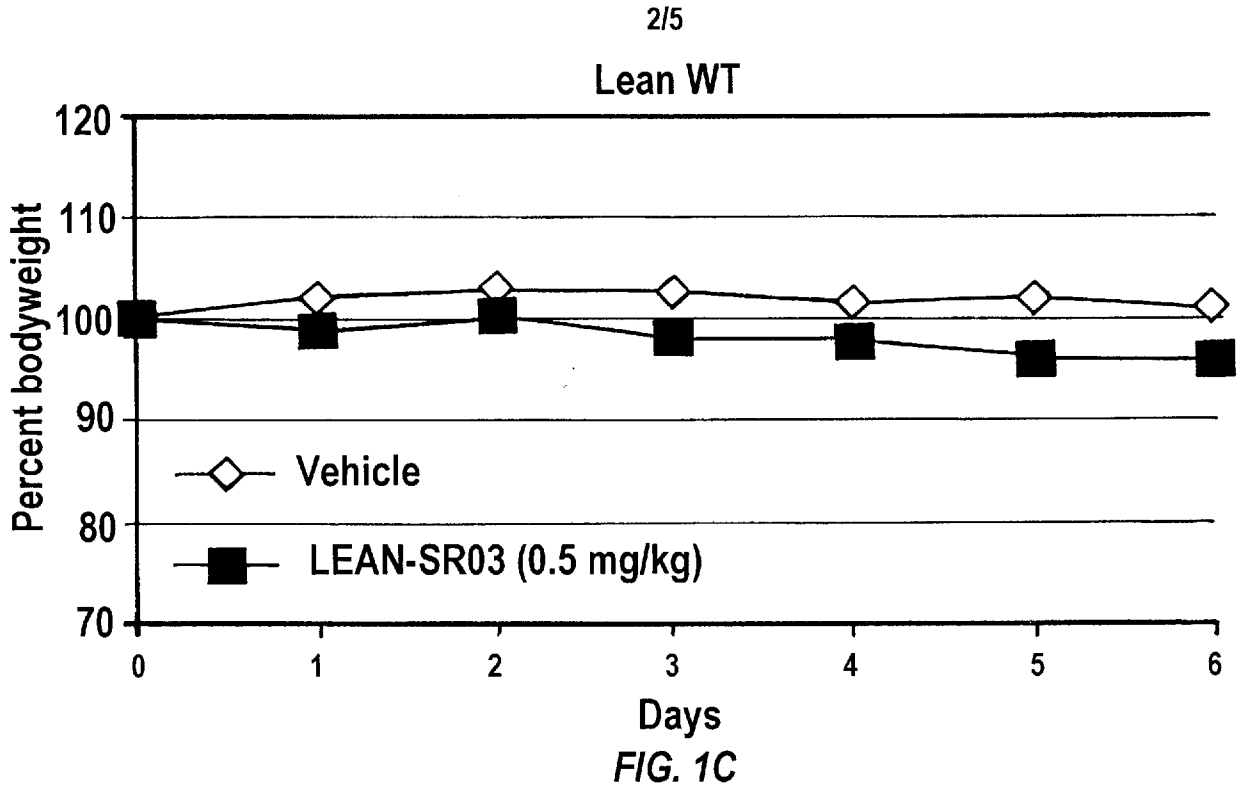


FIG. 1B



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db/db

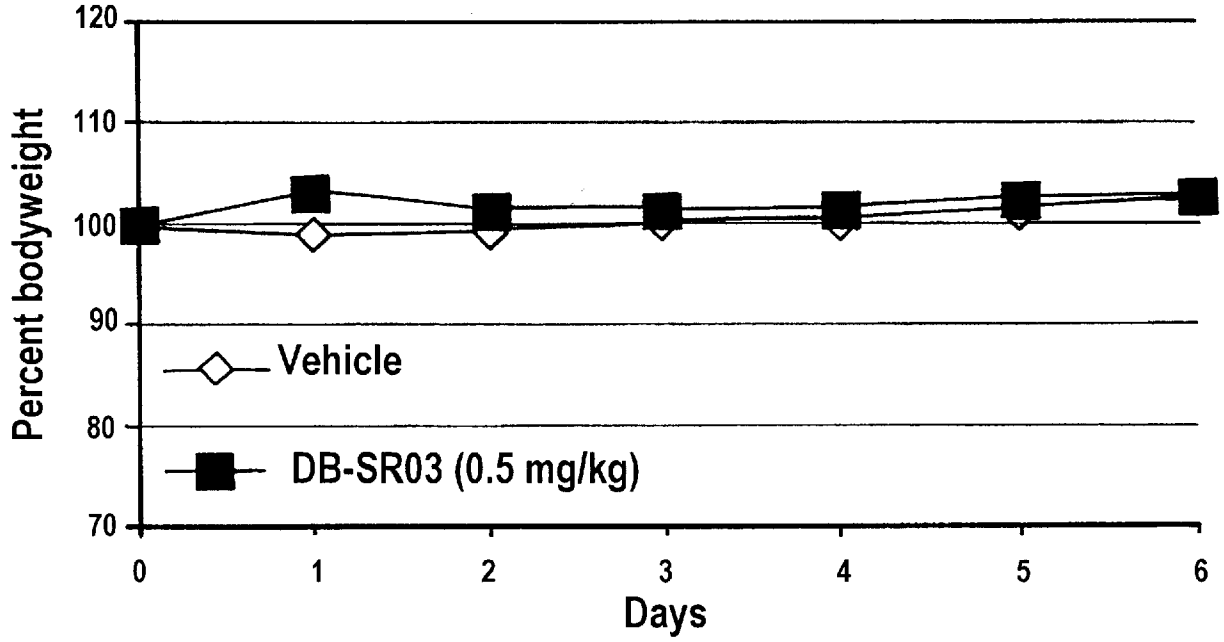


FIG. 1E

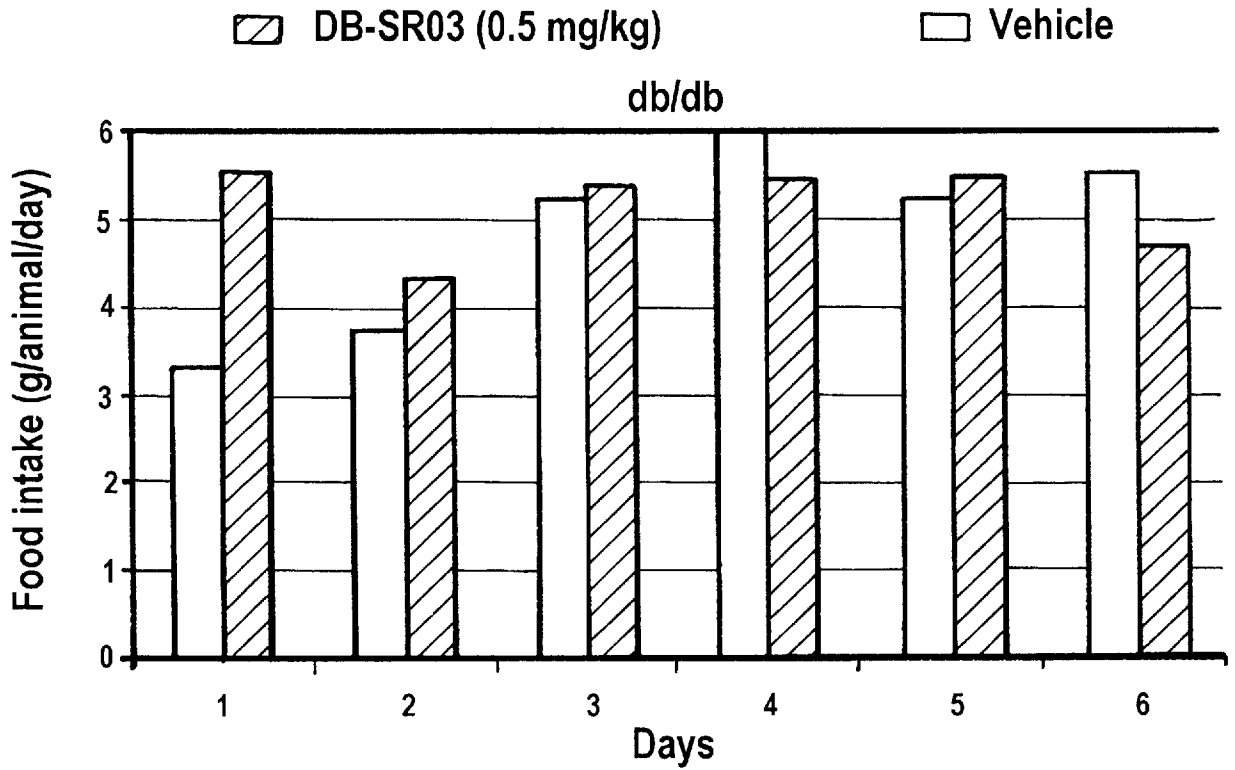


FIG. 1F

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HFD WT

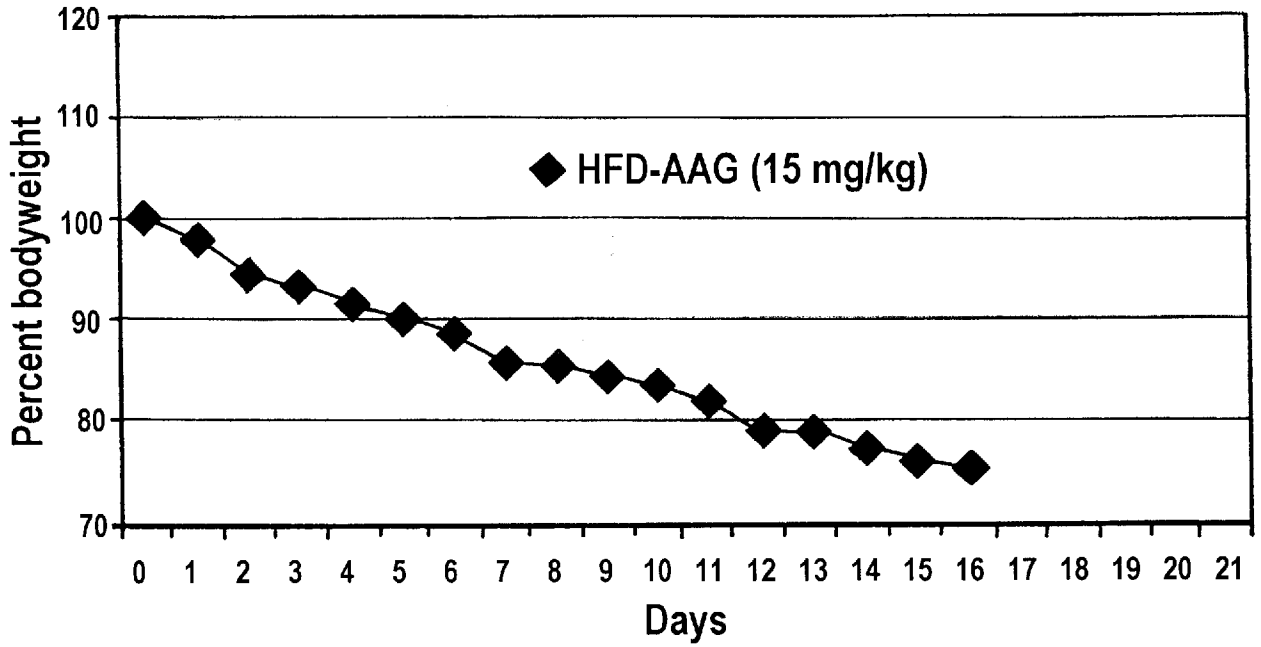


FIG. 2A

Lean WT

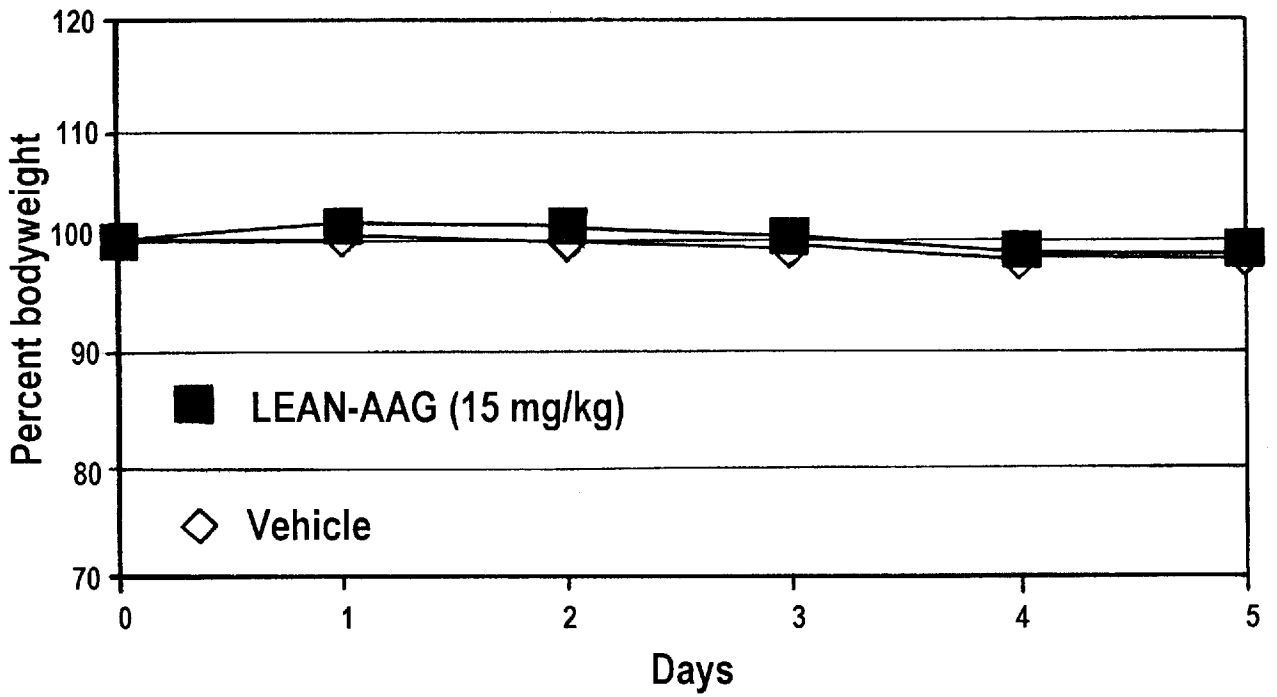


FIG. 2B

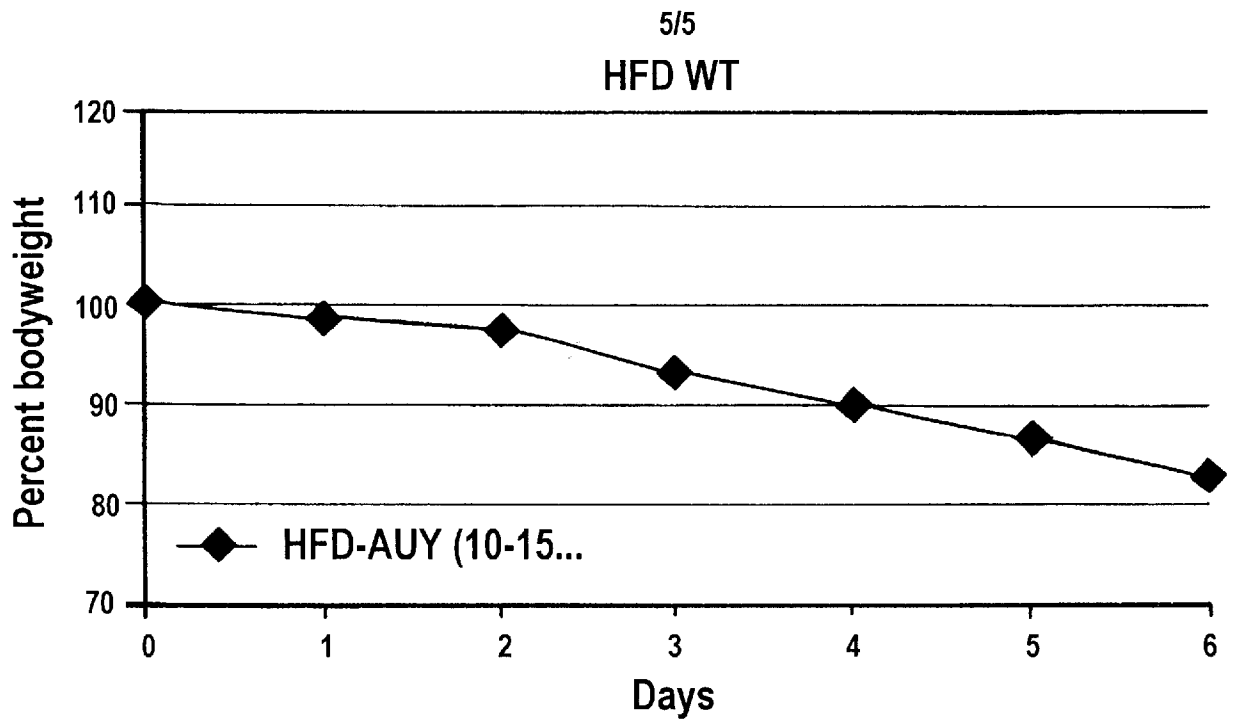


FIG. 3A

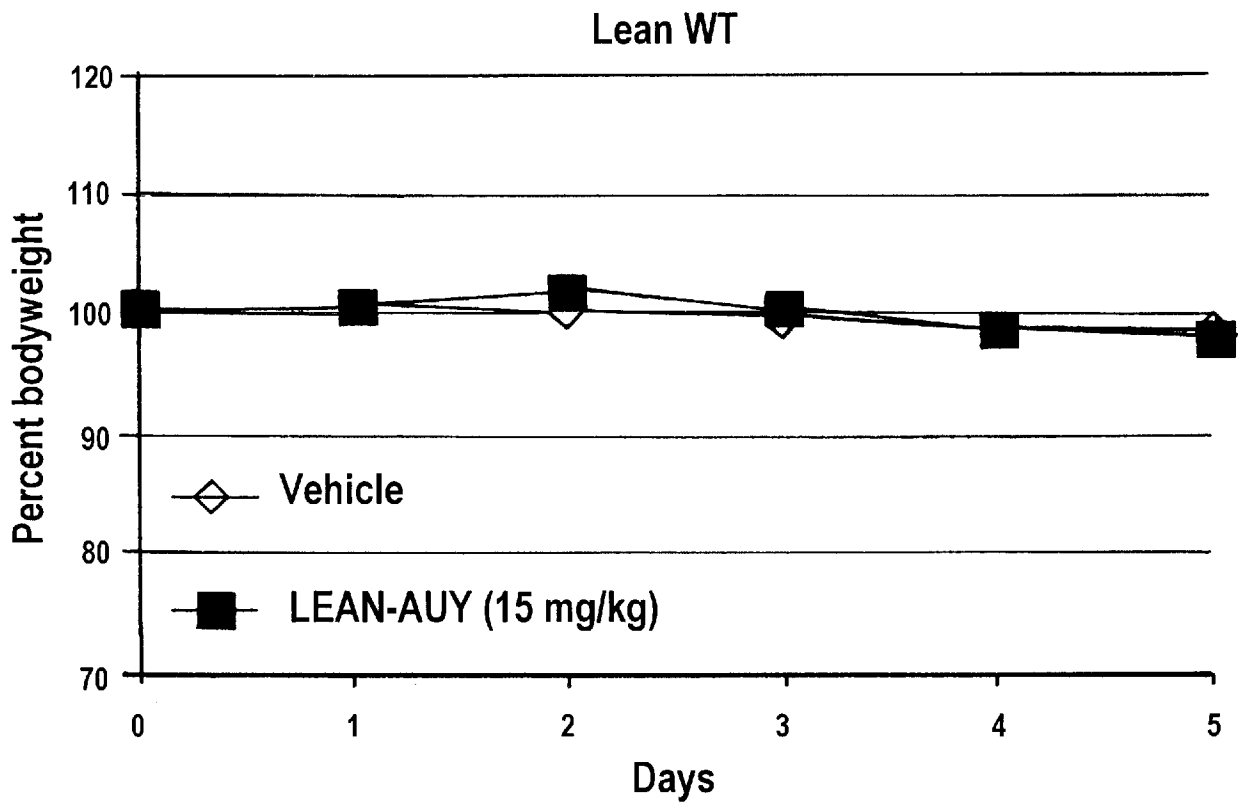


FIG. 3B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/024188

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/352 A61P3/04 A61P3/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61P
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 201322 Thomson Scientific, London, GB; AN 2013-C31957 XP002740298, & CN 102 772 399 A (UNIV XIAMEN) 14 November 2012 (2012-11-14) abstract ----- -/--	1-3,8, 11-24

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 29 May 2015	Date of mailing of the international search report 24/08/2015
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Economou, Dimitrios
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/024188

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HE YONGHAN ET AL: "Radicol, a heat shock protein 90 inhibitor, inhibits differentiation and adipogenesis in 3T3-L1 preadipocytes", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 436, no. 2, 28 May 2013 (2013-05-28), pages 169-174, XP028574166, ISSN: 0006-291X, DOI: 10.1016/J.BBRC.2013.05.068 the whole document abstract page 170, left-hand column, paragraph 1 Discussion; page 172 - page 174</p>	1
X	<p>M T NGUYEN ET AL: "Hsp90 chaperones PPAR[gamma] and regulates differentiation and survival of 3T3-L1 adipocytes", CELL DEATH AND DIFFERENTIATION, vol. 20, no. 12, 4 October 2013 (2013-10-04), pages 1654-1663, XP055191843, ISSN: 1350-9047, DOI: 10.1038/cdd.2013.129 the whole document abstract page 1654, left-hand column, paragraph 1 page 1655, left-hand column, paragraph 2 page 1659, left-hand column, last paragraph - page 1661, left-hand column, paragraph 3</p>	1,2, 11-24
X	<p>BAOBING ZHAO ET AL: "Gambogic acid activates AMP-activated protein kinase in mammalian cells", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 424, no. 1, 1 July 2012 (2012-07-01), pages 100-104, XP055192087, ISSN: 0006-291X, DOI: 10.1016/j.bbrc.2012.06.078 the whole document abstract Introduction; page 100</p>	1-3,8, 11-24
X	<p>US 2005/261363 A1 (LEE SEN-BIN [TW] ET AL) 24 November 2005 (2005-11-24) the whole document claims 3-9</p>	1,2,8
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/024188

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 619 195 A2 (TAIWAN SUNPAN BIOTECHNOLOGY DE [TW]) 25 January 2006 (2006-01-25) the whole document claims 4-14 -----	1,2,8
X	DATABASE WPI Week 200210 Thomson Scientific, London, GB; AN 2002-067408 XP002740299, & CN 1 309 125 A (UNIV CHINA PHARMACY) 22 August 2001 (2001-08-22) abstract -----	1,2,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/024188

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

3, 8(completely); 1, 2, 11-24(partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3, 8(completely); 1, 2, 11-24(partially)

A pharmaceutical composition/method comprising an HSP90 inhibitor to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient wherein the HSP90 inhibitor is a xanthonoid.

2. claims: 4, 5, 9(completely); 1, 2, 11-24(partially)

A pharmaceutical composition/methods comprising an HSP90 inhibitor to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient wherein the HSP90 inhibitor is a benzoquinone ansamycin antibiotic

3. claims: 6, 10(completely); 1, 2, 11-24(partially)

A pharmaceutical composition/methods comprising an HSP90 inhibitor to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient wherein the HSP90 inhibitor is a resorcinol derivative

4. claims: 7(completely); 1, 2, 11-24(partially)

A pharmaceutical composition/methods comprising an HSP90 inhibitor to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient wherein the HSP90 inhibitor is a purine analog.

5. claims: 1, 2, 11-24(all partially)

A pharmaceutical composition/methods comprising an HSP90 inhibitor to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

homeostasis in a pre-obese, obese, or morbidly obese patient
wherein the HSP90 inhibitor is SNX- 5422

6. claims: 1, 2, 11-24(all partially)

A pharmaceutical composition/methods comprising an HSP90 inhibitor to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient wherein the HSP90 inhibitor is DS-2248.

7. claims: 1, 2, 11-24(all partially)

A pharmaceutical composition/methods comprising an HSP90 inhibitor to induce weight loss in a pre-obese, obese, or morbidly obese patient; reduce body fat in a pre-obese, obese, or morbidly obese patient; reduce food intake in a pre-obese, obese, or morbidly obese patient; improve glucose homeostasis in a pre-obese, obese, or morbidly obese patient wherein the HSP90 inhibitor is XL-888.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/024188

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 102772399	A	14-11-2012	NONE

US 2005261363	A1	24-11-2005	JP 4425109 B2 03-03-2010
			JP 2005330261 A 02-12-2005
			JP 2009280610 A 03-12-2009
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CN 1309125	A	22-08-2001	NONE
