(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 March 2017 (23.03.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/048670 A1

(51) International Patent Classification:
A61K 31/137 (2006.01) *A61P 9/12* (2006.01)
A61K 31/7042 (2006.01) *A61P 13/00* (2006.01)
A61P 3/04 (2006.01) *A61P 1/16* (2006.01)
A61P 3/00 (2006.01) *A61P 43/00* (2006.01)
A61P 9/00 (2006.01)

(21) International Application Number:
PCT/US2016/051435

(22) International Filing Date:
13 September 2016 (13.09.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/218,842 15 September 2015 (15.09.2015) US
62/306,110 10 March 2016 (10.03.2016) US
15/262,038 12 September 2016 (12.09.2016) US

(71) Applicant: **JANSSEN PHARMACEUTICA NV** [BE/BE]; Turnhoutseweg 30, 2340 Beerse (BE).

(72) Inventor; and
(71) Applicant *(for US only)*: **ROSENTHAL, Norman R.** [US/US]; 920 US Highway 202 S, Raritan, New Jersey 08869 (US).

(72) Inventors: **ROTHENBERG, Paul**; 920 US Highway 202 S, Raritan, New Jersey 08869 (US). **POLIDORI, David C.**; 3210 Merryfield Row, San Diego, California 92121 (US). **WAYS, Douglas K.**; 920 US Highway 202 S, Raritan, New Jersey 08869 (US). **STEIN, Peter P.**; 19 Birchwood Court, Princeton, New Jersey 08550 (US).

(74) Agents: **SHIRTZ, Joseph F.** et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,

[Continued on next page]

(54) Title: CO-THERAPY COMPRISING CANAGLIFLOZIN AND PHENTERMINE FOR THE TREATMENT OF OBESITY AND OBESITY RELATED DISORDERS

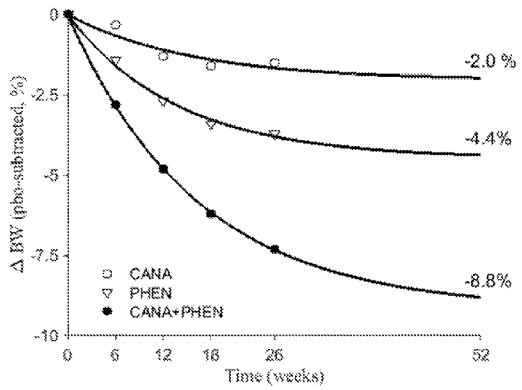


Figure 1: Mean placebo-subtracted weight loss (measured at 0-26 Weeks, extrapolated to 52 Weeks) for Canagliflozin, Phentermine and Combiantion Therapy

(57) Abstract: The present invention is directed to the use of co-therapy comprising administration of canagliflozin and phentermine for the treatment of obesity and obesity related disorders. More particularly, the present invention is directed to co-therapy for treating obesity, for promoting weight loss and/or for suppressing appetite; for treating, delaying, slowing the progression of and/or preventing metabolic disorders (including for example Type 2 diabetes mellitus); for treating, delaying, slowing the progression of and/or preventing renal or fatty liver disorders (including for example NASH, NAFLD, etc.); for treating, delaying, slowing the progression of and/or preventing sleep disorders (including for example sleep apnea); for providing cardiovascular protection; for treating, delaying, slowing the progression of and/or preventing cardiovascular events (including major adverse cardiac events (MACE) such as myocardial infarction, unstable angina, cardiovascular death, revascularization, fatal or non-fatal cerebrovascular accident, peripheral arteriopathy, aortic events, hospitalization due to congestive heart failure, etc.); and/or for extending or prolonging life span.

WO 2017/048670 A1

DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

CO-THERAPY COMPRISING CANAGLIFLOZIN AND PHENTERMINE FOR THE TREATMENT OF OBESITY AND OBESITY RELATED DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This Application claims priority to United States Provisional Patent Application No. 62/218,842, filed September 15, 2015, and United States Provisional Patent Application No. 62/306,110, filed March 10, 2016, the disclosures of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention is directed to the use of co-therapy comprising administration of canagliflozin and phentermine for the treatment of obesity and obesity related disorders. More particularly, the present invention is directed to co-therapy for treating obesity, for promoting weight loss and/or for suppressing appetite; for treating, delaying, slowing the progression of and / or preventing metabolic disorders (including for example Type 2 diabetes mellitus); for treating, delaying, slowing the progression of and / or preventing renal or fatty liver disorders (including for example NASH, NAFLD, etc.); for treating, delaying, slowing the progression of and / or preventing sleep disorders (including for example sleep apnea); for providing cardiovascular protection; for treating, delaying, slowing the progression of and / or preventing cardiovascular events (including major adverse cardiac events (MACE) such as myocardial infarction, unstable angina, cardiovascular death, revascularization, fatal or non-fatal cerebrovascular accident, peripheral arteriopathy, aortic events, hospitalization due to congestive heart failure, etc.); and/or for extending or prolonging life span.

BACKGROUND OF THE INVENTION

Obesity is a state of excess adipose tissue mass. Although often viewed as equivalent to increased body weight, this need not be the case-lean but very muscular individuals may be overweight by arbitrary standards without having increased adiposity. Body weights are distributed continuously in populations, so that a medically meaningful distinction between lean and obese is somewhat

arbitrary. Obesity is therefore more effectively defined by assessing its linkage to morbidity or mortality.

Although not a direct measure of adiposity, the most widely used method to gauge obesity is the *body mass index* (BMI), which is equal to weight/height^2 (in kg/m^2). Other approaches to quantifying obesity include anthropometry (skin-fold thickness), densitometry (underwater weighing), computed tomography (CT) or magnetic resonance imaging (MRI), and electrical impedance. Using data from the Metropolitan Life Tables, BMIs for the midpoint of all heights and frames among both men and women range from 19 to 26 kg/m^2; at a similar BMI, women have more body fat than men. Based on unequivocal data of substantial morbidity, a BMI of 30 is most commonly used as a threshold for obesity in both men and women. Large-scale epidemiologic studies suggest that all-cause, metabolic, and cardiovascular morbidity begin to rise (albeit at a slow rate) when BMIs are ≥25, suggesting that the cut-off for obesity should be lowered. Some authorities use the term overweight (rather than obese) to describe individuals with BMIs between 25 or 27 and 30. A BMI between 25 and 30 should be viewed as medically significant and worthy of therapeutic intervention, especially in the presence of risk factors that are influenced by adiposity, such as hypertension and glucose intolerance.

Recent data from the National Health and Nutrition Examination Surveys (NHANES) show that the percent of the American adult population with obesity (BMI > 30) has increased from 14.5% (between 1976 and 1980) to 22.5% (between 1998 and 1994). As many as 50% of U.S. adults ≥20 years of age were overweight (defined as BMI > 25) between the years of 1998 and 1991. Because substantial health risks exist in many individuals with BMI between 25 and 30, the increasing prevalence of medically significant obesity raises great concern. Obesity is more common among women and in the poor; the prevalence in children is also rising at a worrisome rate.

Obesity has major adverse effects on health. Morbidly obese individuals (>200% ideal body weight) have as much as a twelve-fold increase in mortality. Mortality rates rise as obesity increases, particularly when obesity is associated with increased intra-abdominal fat. It is also apparent that the degree to which obesity affects particular organ systems is influenced by susceptibility genes

that vary in the population. Obese individuals have a 50-100% increased risk of premature death from all causes compared to individuals with normal body weight. Over 300,000 deaths a year in the United States may be attributable to obesity.

Patients with obesity also have a higher chance of developing insulin resistance or glucose intolerance, which can progress to the development of type-2 diabetes. There is also a higher probability of high blood pressure, sexual dysfunction, headaches, depression and sleep apnea.

Diabetes mellitus is a medical term for the presence of elevated blood glucose. People with diabetes either don't produce insulin, produce too little insulin or do not respond to insulin, resulting in the build up of glucose in the blood. The most common form of diabetes is Type 2 diabetes, once referred to as adult onset diabetes or non-insulin dependent diabetes (NIDDM), which may account for >90% of diabetes in adults. However, as the younger population becomes increasingly overweight or obese, Type 2 diabetes is becoming more prevalent in teens and children. Diabetes may also refer to gestational diabetes, Type 1 diabetes or autoimmune diabetes, once referred to as juvenile onset diabetes and type 1 1/2 diabetes, also referred to as latent-autoimmune diabetes in adults or LADA. Diabetes may occur because of poor dietary habits or lack of physical activity (e.g., sedentary lifestyle), genetic mutations, injury to the pancreas, drug (e.g., AIDS therapies) or chemical (e.g., steroid) exposure or disease (e.g., cystic fibrosis, Down syndrome, Cushing's syndrome). Two rare types of genetic defects leading to diabetes are termed maturity-onset diabetes of the young (MODY) and atypical diabetes mellitus (ADM).

Type II diabetes mellitus (non-insulin-dependent diabetes mellitus or NIDDM) is a metabolic disorder involving disregulation of glucose metabolism and insulin resistance, and long-term complications involving the eyes, kidneys, nerves, and blood vessels. Type II diabetes mellitus usually develops in adulthood (middle life or later) and is described as the body's inability to make either sufficient insulin (abnormal insulin secretion) or its inability to effectively use insulin (resistance to insulin action in target organs and tissues). More

particularly, patients suffering from Type II diabetes mellitus have a relative insulin deficiency. That is, in these patients, plasma insulin levels are normal to high in absolute terms, although they are lower than predicted for the level of plasma glucose that is present.

Type II diabetes mellitus is characterized by the following clinical signs or symptoms: persistently elevated plasma glucose concentration or hyperglycemia; polyuria; polydipsia and / or polyphagia; chronic microvascular complications such as retinopathy, nephropathy and neuropathy; and macrovascular complications such as hyperlipidemia and hypertension which can lead to blindness, end-stage renal disease, limb amputation and myocardial infarction.

Syndrome X, also termed Insulin Resistance Syndrome (IRS), Metabolic Syndrome, or Metabolic Syndrome X, is a disorder that presents risk factors for the development of Type II diabetes mellitus and cardiovascular disease including glucose intolerance, hyperinsulinemia and insulin resistance, hypertriglyceridemia, hypertension and obesity.

The diagnosis of Type II diabetes mellitus includes assessment of symptoms and measurement of glucose in the urine and blood. Blood glucose level determination is necessary for an accurate diagnosis. More specifically, fasting blood glucose level determination is a standard approach used. However, the oral glucose tolerance test (OGTT) is considered to be more sensitive than fasted blood glucose level. Type II diabetes mellitus is associated with impaired oral glucose tolerance (OGT). The OGTT thus can aid in the diagnosis of Type II diabetes mellitus, although generally not necessary for the diagnosis of diabetes (Emancipator K, Am J Clin Pathol 1999 Nov; 112(5):665-74; Type 2 Diabetes Mellitus, Decision Resources Inc., March 2000). The OGTT allows for an estimation of pancreatic beta-cell secretory function and insulin sensitivity, which helps in the diagnosis of Type II diabetes mellitus and evaluation of the severity or progression of the disease (e.g., Caumo A, Bergman RN, Cobelli C,. J Clin Endocrinol Metab 2000, 85(11):4396-402). More particularly, the OGTT is extremely helpful in

establishing the degree of hyperglycemia in patients with multiple borderline fasting blood glucose levels that have not been diagnosed as diabetics. In addition, the OGTT is useful in testing patients with symptoms of Type II diabetes mellitus where the possible diagnosis of abnormal carbohydrate metabolism has to be clearly established or refuted.

Thus, impaired glucose tolerance is diagnosed in individuals that have fasting blood glucose levels less than those required for a diagnosis of Type II diabetes mellitus, but have a plasma glucose response during the OGTT between normal and diabetics. Impaired glucose tolerance is considered a prediabetic condition, and impaired glucose tolerance (as defined by the OGTT) is a strong predictor for the development of Type II diabetes mellitus (Haffner SM, Diabet Med 1997 Aug;14 Suppl 3:S12-8).

Type II diabetes mellitus is a progressive disease associated with the reduction of pancreatic function and/or other insulin-related processes, aggravated by increased plasma glucose levels. Thus, Type II diabetes mellitus usually has a prolonged prediabetic phase and various pathophysiological mechanisms can lead to pathological hyperglycemia and impaired glucose tolerance, for instance, abnormalities in glucose utilization and effectiveness, insulin action and/or insulin production in the prediabetic state (Goldberg RB, Med Clin North Am 1998 Jul;82(4):805-21).

The prediabetic state associated with glucose intolerance can also be associated with a predisposition to abdominal obesity, insulin resistance, hyperlipidemia, and high blood pressure, that is, Syndrome X (Groop L, Forsblom C, Lehtovirta M, Am J Hypertens 1997 Sep;10(9 Pt 2):172S-180S; Haffner SM, J Diabetes Complications 1997 Mar-Apr;11(2):69-76; Beck-Nielsen H, Henriksen JE, Alford F, Hother-Nielson O, Diabet Med 1996 Sep;13(9 Suppl 6):S78-84).

Thus, defective carbohydrate metabolism is pivotal to the pathogenesis of Type II diabetes mellitus and impaired glucose tolerance (Dinneen SF, Diabet Med 1997 Aug;14 Suppl 3:S19-24). In fact, a continuum from impaired glucose tolerance and impaired fasting glucose to definitive Type II diabetes

mellitus exists (Ramlo-Halsted BA, Edelman SV, Prim Care 1999 Dec;26(4):771-89).

Early intervention in individuals at risk to develop Type II diabetes mellitus, focusing on reducing the pathological hyperglycemia or impaired glucose tolerance may prevent or delay the progression towards Type II diabetes mellitus and associated complications and/or Syndrome X. Therefore, by effectively treating impaired oral glucose tolerance and / or elevated blood glucose levels, one can prevent or inhibit the progression of the disorder to Type II diabetes mellitus or Syndrome X.

Kidneys are bean-shaped organs, located near the middle of the back. Inside each kidney about a million tiny structures called nephrons filter blood. They remove waste products and extra water, which become urine. Damage to the nephrons represents an important form of kidney disease. This damage may leave kidneys unable to remove wastes. Some damage, e.g. damage related to hyperfiltration can occur slowly over years, initially often without obvious symptoms.

The 'hyperfiltrative hypothesis' implies that the excess demand on a limited renal reserve produces adaptive and ultimately pathologic changes in the kidney which finally lead to 'nephron exhaustion'. At the single-nephron level, hyperfiltration is hypothesized to be an early link in the chain of events that lead from intraglomerular hypertension to albuminuria and, subsequently, to reduced Glomerular Filtration Rate (GFR). Based on this hyperfiltration therefore represents a risk for subsequent renal injury and could be classified as an early manifestation of renal pathology often referred to as the hyperfiltrative stage. Such renal hyperfiltration can lead to early glomerular lesions and to microalbuminuria, which itself can lead to macroalbuminuria and to end-stage renal disease.

The influence of hyperfiltration on renal function decline has been most thoroughly evaluated in kidney transplant recipients and donors, and in patients with a single kidney removed for acquired renal disease, but also in patients with diabetes mellitus (Magee et al. Diabetologia 2009; 52: 691-697). In theory,

any reduction in functional nephron number will lead to adaptive glomerular hyperfiltration whether induced genetically, surgically, or by acquired renal disease. Moreover, hyperfiltration has been shown to occur in certain pathophysiologic conditions even when renal mass is intact, e.g. in diabetes. Therefore, there is a medical need for interventions with a good efficacy with regard to renal hyperfiltrative injury.

Creatinine is a breakdown product of creatine phosphate in muscle tissue, and is usually produced at a constant rate in the body. Serum creatinine is an important indicator of renal health, because it is an easily measured byproduct of muscle metabolism that is excreted unchanged by the kidneys. Creatinine is removed from the blood chiefly by the kidneys, primarily by glomerular filtration, but also by proximal tubular secretion. Little or no tubular reabsorption of creatinine occurs. If the filtration in the kidney is deficient, creatinine blood levels rise. Therefore, creatinine levels in blood and urine may be used to calculate the creatinine clearance (CrCl), which correlates with the glomerular filtration rate (GFR). Blood creatinine levels may also be used alone to estimate the GFR (eGFR). The GFR is clinically important because it is a measurement of renal function. An alternate estimation of renal function can be made when interpreting the blood (plasma) concentration of creatinine along with that of urea. The BUN-to-creatinine ratio (the ratio of blood urea to creatinine) can indicate other problems besides those intrinsic to the kidney; for example, a urea level raised out of proportion to the creatinine may indicate a pre-renal problem such as volume depletion.

A rise in blood creatinine level is observed only with marked damage to functioning nephrons. An estimation of kidney function is given by calculating the estimated glomerular filtration rate (eGFR). eGFR can be accurately calculated using serum creatinine concentration. The typical human reference ranges for serum creatinine are 0.5 to 1.0 mg/dl (about 45-90 µmol/l) for women and 0.7 to 1.2 mg/dl (60-110 µmol/l) for men. The trend of serum creatinine levels over time is generally more important than absolute creatinine level.

Creatinine levels may increase modestly when an ACE inhibitor (ACEi) or angiotensin II receptor antagonist (or angiotensin receptor blocker, ARB) is taken. Using both an ACE inhibitor and ARB concomitantly will increase creatinine levels to a greater degree than either of the two drugs would individually. An increase of <30% is to be expected with ACE inhibitor or ARB use.

Albuminuria is a condition, where albumin is present in the urine. In healthy individuals, albumin is filtered by the kidneys. When the kidneys do not properly filter large molecules (such as albumin) from the urine, albumin is excreted in urine and is typically a sign of kidney damage or excessive salt intake. Albuminuria can also occur in patients with long-standing diabetes mellitus, either Type I (1) or Type II (2) diabetes mellitus. Urine albumin may be measured by dipstick or as direct measure of the amount of protein excreted in total volume of urine collected over a 24 hour period

Microalbuminuria, occurs when the kidney leaks small amounts of albumin into the urine, as a result of an abnormally high permeability for albumin in the renal glomerulus. Microabuminuria as a condition of diabetic nephropathy is indicated when urine albumin levels are in the range of 30 mg to 300 mg in a 24 hour period.

An alternate measure of microalbuminuria is creatinine levels and the ratio of albumin to creatinine in serum. The albumin/creatinine ratio (ACR) and microalbuminuria are defined as ACR ≥3.5 mg/mmol (female) or ≥2.5 mg/mmol (male), or, with both substances measured by mass, as an ACR between 30 µg albumin/mg creatinine and 300 µg albumin/mg creatinine.

Microalbuminuria may be an important prognostic marker for the development and progression of kidney disease, particularly in patients with diabetes mellitus or hypertension. Microalbuminuria is also an indicator of subclinical cardiovascular disease, a marker of vascular endothelial dysfunction and a risk factor for venous thrombosis.

Diabetic nephropathy is one of the microvascular complications of diabetes mellitus and is characterized by persistent albuminuria and a

progressive decline in renal function. Hyperglycemia is an important contributor to the onset and progression of diabetic nephropathy.

The clinical progression of diabetic nephropathy in patients with T1DM (Type 1 Diabetes Mellitus) is well characterized. Initially, hyperfiltration accompanied by increases in glomerular filtration rate (GFR) and increased renal plasma flow is seen. A meta-analysis found that the presence of hyperfiltration in patients with T1DM more than doubled the risk of developing micro- or macroalbuminuria. This phase is followed by reductions in GFR and the development of microalbuminuria, defined as urinary albumin excretion of ≥30 mg/day (or 20 µg/min) and <300 mg/24 h (or <200 µg/min), which may be accompanied by increases in blood pressure. Later in the progression of the disease as GFR continues to decline, overt proteinuria (i.e., macroalbuminuria), defined as urinary albumin excretion of >300 mg/day ensues and is associated with worsening hypertension. Eventually, ESKD (End Stage Kidney Disease) progresses, leading to the need for renal replacement therapy.

In patients with Type 2 Diabetes Mellitus (T2DM), the clinical progression is variable, primarily due to multiple renal insults, including not only hyperglycemia, but also vascular pathology resulting in ischemic renal injury. However, other common features are likely to contribute to renal injury in patients with T2DM include hyperfiltration at the level of the single nephron, proximal tubular glucotoxicity, and a stimulus for tubular cell growth as a result of enhanced sodium coupled glucose transport into tubular cells.

Studies have demonstrated that albuminuria is a biomarker for predicting progression of diabetic nephropathy and is a cardiovascular (CV) risk factor. When compared with patients with normo-albuminuria and estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73m^2, patients with both macroalbuminuria and eGFR <60 mL/min/1.73m^2 were at 5.9-fold higher risk (95% CI 3.5 to 10.2) for cardiovascular death and 22.2-fold higher risk (95% CI 7.6 to 64.7) for experiencing ESKD, and subjects with macroalbuminuria and reduced eGFR (ie, <60 mL/min/1.73m^2) were nearly 6 times more likely to experience a composite renal event (i.e., death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine. See, e.g., J Am Soc Nephrol 20(8):1813-1821, 2009. A close link between the

degree of albuminuria and CV disease has also been demonstrated in the RENAAL study, showing that patients with high baseline urinary albumin/creatinine ratio (ACR) (≥3 g/g) had a 1.2-fold (95% CI, 1.54 to 2.38) higher risk of a composite of myocardial infarction (MI), stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or CV death, and a 2.7-fold (95% CI, 1.94 to 3.75) higher risk of heart failure compared with patients with an ACR <1.5 g/g. Increased urinary albumin excretion and reduced eGFR are also independently associated with the risk for both cardiovascular and kidney outcomes in patients with T2DM, without evidence for an interaction between these risk factors. Moderately increased albuminuria also has been associated with an increase in renal disease progression.

In summary, the magnitude of albuminuria positively correlates with the development of ESKD and adverse CV outcomes. Treatment-related reductions in albuminuria in patients with T2DM and albuminuria using agents acting by a hemodynamic mechanism (i.e., ACEi and ARBs) are correlated with reductions in the progression of diabetic nephropathy and in the incidence of adverse CV outcomes. Thus, agents acting by a unique hemodynamic mechanism to reduce albuminuria beyond that seen with other antihypertensive or antihyperglycemic agents and which are additive to agents disrupting the renin-angiotensin system may exert reno-protective effects and possibly reduce adverse CV outcomes in diabetic nephropathy.

Fatty liver, also known as fatty liver disease (FLD), is a reversible condition wherein large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis (i.e., abnormal retention of lipids within a cell). Accumulation of fat may also be accompanied by a progressive inflammation of the liver (hepatitis), called steatohepatitis. By considering the contribution by alcohol, fatty liver may be termed alcoholic steatosis or non-alcoholic fatty liver disease (NAFLD), and the more severe forms as alcoholic steatohepatitis (part of alcoholic liver disease) and non-alcoholic steatohepatitis (NASH).

Non-alcoholic fatty liver disease (NAFLD) is one cause of a fatty liver, occurring when fat is deposited (steatosis) in the liver. NAFLD is considered to

cover a spectrum of disease activity. This spectrum begins as fatty accumulation in the liver (hepatic steatosis). A liver can remain fatty without disturbing liver function, but by varying mechanisms and possible insults to the liver may also progress to become NASH, a state in which steatosis is combined with inflammation and fibrosis. Non-alcoholic steatohepatitis (NASH) is a progressive, severe form of NAFLD. Over a 10-year period, up to 20% of patients with NASH will develop cirrhosis of the liver, and 10% will suffer death related to liver disease. The exact cause of NAFLD is still unknown, however, both obesity and insulin resistance are thought to play a strong role in the disease process. The exact reasons and mechanisms by which the disease progresses from one stage to the next are not known.

NAFLD has been linked to insulin resistance (IR) and the metabolic syndrome (MS). As the renin-angiotensin system (RAS) plays a central role in insulin resistance, and subsequently in NAFLD and NASH, an attempt to block the deleterious effects of RAS overexpression has been proposed a target for treatment. While many potential therapies tested in NASH target only the consequences of this condition, or try to “get rid” of excessive fat, angiotensin receptor blockers (ARBs) may act as a tool for correction of the various imbalances that act in harmony in NASH / NAFLD. Indeed, by inhibiting RAS the intracellular insulin signaling pathway may be improved, resulting in better control of adipose tissue proliferation and adipokine production, as well as more balanced local and systemic levels of various cytokines. At the same time, by controlling the local RAS in the liver fibrosis may be prevented and the cycle that links steatosis to necroinflammation slowed down. (GEORGESCU, E.F., in Advances in Therapy, 2008, pp 1141-1174, Vol. 25, Issue 11)

Sleep apnea is a sleep disorder characterized by pauses in breathing or instances of shallow or infrequent breathing during sleep. Each pause in breathing, called an apnea, can last for several seconds to several minutes, and may occur, by definition, at least 5 times in an hour. Similarly, each abnormally shallow breathing event is called a hypopnea. Sleep apnea is classified as a dyssomnia, meaning abnormal behavior or psychological events

occur during sleep. When breathing is paused, carbon dioxide builds up in the bloodstream. Chemoreceptors in the blood stream note the high carbon dioxide levels. The brain is signaled to wake the person sleeping and breathe in air. Breathing normally will restore oxygen levels and the person will fall asleep again. Sleep apnea is often diagnosed with an overnight sleep test or "sleep study".

There are three forms of sleep apnea: central (CSA), obstructive (OSA) and complex or mixed sleep apnea (i.e., a combination of central and obstructive) constituting 0.4%, 84%, and 15% of cases, respectively. In CSA, breathing is interrupted by a lack of respiratory effort; in OSA, breathing is interrupted by a physical block to airflow despite respiratory effort, and snoring is common. According to the NIH, 12 million Americans have OSA. There are more cases of sleep apnea still because people either do not report the condition or do not know they have sleep apnea.

Regardless of type, an individual with sleep apnea is rarely aware of having difficulty breathing, even upon awakening. Sleep apnea is recognized as a problem by others witnessing the individual during episodes or is suspected because of its effects on the body. Symptoms may be present for years (or even decades) without identification, during which time the person may become conditioned to the daytime sleepiness and fatigue associated with sleep disturbance. Sleep apnea affects not only adults but some children as well.

Symptoms of sleep apnea include excessive daytime sleepiness (EDS) and impaired alertness. In other words, common effects of sleep apnea include daytime fatigue, a slower reaction time, and vision problems. OSA may increase risk for driving accidents and work-related accidents. If OSA is not treated, one has an increased risk of other health problems such as diabetes. Even death could occur from untreated OSA due to lack of oxygen to the body. Moreover, people with sleep apnea are examined using "standard test batteries" in order to further identify parts of the brain that may be adversely affected by sleep apnea, including those that govern: "executive functioning", the way the person plans and initiates tasks; attention, working effectively and processing information when in a waking state; using memory and learning.

Due to the disruption in daytime cognitive state, behavioral effects are also present. These include moodiness, belligerence, as well as a decrease in attentiveness and drive. Another symptom of sleep apnea is waking up in sleep paralysis. In severe cases, the fear of sleep due to sleep paralysis can lead to insomnia. These effects become very hard to deal with, thus the development of depression may transpire.

There is some evidence that the risk of diabetes among those with moderate or severe sleep apnea is higher. There is also increasing evidence that sleep apnea may also lead to liver function impairment, particularly fatty liver diseases.

Sleep apnea can affect people regardless of sex, race, or age. Risk factors include being male, overweight, obese, or over the age of 40; or having a large neck size (greater than 16–17 inches), enlarged tonsils, enlarged tongue, small jaw bone, gastroesophageal reflux, allergies, sinus problems, family history of sleep apnea, or deviated septum causing nasal obstruction. Alcohol, sedatives and tranquilizers also promote sleep apnea by relaxing the throat. People who smoke have sleep apnea at three times the rate of people who have never smoked. All the factors above may contribute to obstructive sleep apnea. Central sleep apnea is more influenced by being male, being older than 65 years, having heart disorders such as atrial fibrillation, and stroke or brain tumor. Brain tumors may hinder the brain's ability to regulate normal breathing. High blood pressure is also very common in people with sleep apnea.

In adults, the most common cause of OSA is excess weight and obesity, which is associated with soft tissue of the mouth and throat. During sleep, when throat and tongue muscles are more relaxed, this soft tissue can cause the airway to become blocked. In children, causes of OSA often include enlarged tonsils or adenoids, and dental conditions such as a large overbite. Less common causes include a tumor or growth in the airway, and birth defects such as Down syndrome and Pierre-Robin syndrome. Although childhood obesity may cause OSA, it is much less commonly associated with the condition than adult obesity.

For many patients with sleep disorders, including sleep apena, the first and best treatment is weight loss. Although not everyone with sleep apnea is overweight, but most patients are and it is theorized that losing weight helps eliminate fat that blocks the windpipe, resulting in the sleep apnea.

Caloric restriction (CR) increases lifespan and slows age-related degenerative changes in many species, including yeast, worms, flies, rodents, monkeys and perhaps humans. Caloric restriction influences certain signaling pathways that regulate key cell functions, including the insulin/insulin-like growth factor-1 pathway, the nutrient-responsive 'target of rapamycin (TOR)' pathway, and also the activity of protein deacetylase enzymes. Certain protein deacetylases regulate the DNA-binding activity of histone proteins, which in turn, regulates the transcription and expression of specific genes, thus affecting cell and organ functions.

Caloric restriction, like fasting, triggers utilization of stored fat reserves as an energy source. Fat oxidation leads to elevated circulating levels of ketone bodies – small metabolites, such as acetoacetate and beta-hydroxybutyrate (BOHB) – which are used as an alternative energy source by some tissues, such as the brain, when glucose levels are low (NEWMAN, J.C., et al., Ketone bodies as signaling metabolites, Trends Endocrinology and Metabolism, 2014, pp42 Vol 25, Issue 1).

Recently published data indicates that BOHB is not simply an alternative metabolic fuel, but unexpectedly also has specific cell signaling and regulatory actions; actions that may mediate certain of the longevity-promoting effects associated with caloric restriction. In particular, BOHB has been shown to directly inhibit certain histone deacetylase enzymes (HDACs), and BOHB treatment of cultured cells increases histone acetylation, similar that observed with fasting in animals (SHIMAZU, T. et al. Suppression of Oxidative Stress by Beta-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor, Science, 2013, pp211 Vol. 339). BOHB treatment of mice increases histone acetylation and thereby alters expression of certain genes associated with resistance to oxidative stress, notably the FOXO3 gene, a mammalian version of the transcription factor DAF16 that is a key regulator of lifespan in worms. HDAC

inhibition by BOHB may also regulate the acetylation state and activity of non-histone proteins that also have cell protective effects.

Recently, BOHB was reported to inhibit the NLRP3 inflammasome, a sensor of the innate immune system which normally triggers inflammatory responses to a variety of injurious agents, such as excess glucose, urate, and amyloids that are associated with some chronic diseases. The known anti-inflammatory effects of fasting or ketogenic diets have been attributed to this effect of BOHB (YOUM, Y.H., et al., The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease, Nature Medicine, 2015, pp263, Vol. 21, Issue 3).

Published data also indicates that BOHB binds to two specific cell-surface receptors (GPR109 and GPR41; TAGGART, A.K., et al., D-Beta-Hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMB-G, J. Biol. Chem., 2005, pp26649, Vol. 280; and KIMURA, I., et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via GPR41, Proc. Natl. Acad. Sci. USA, 2011, pp8030, Vol. 108). BOHB binding to GPR41, a G-protein coupled receptor expressed in sympathetic neurons, suppresses sympathetic activity, reduces fat oxidation, and reduces overall metabolic rate in mice. In the worm (*C. elegans*), BOHB treatment is reported to increase lifespan by ~20% (EDWARDS, C., et al., D-Beta-Hydroxybutyrate extends lifespan in C. elegans, Aging, 2014, pp621, Vol. 6, Issue 8).

Fasting is not the only means to elevate ketone body levels. Ketogenic diets - which reduce carbohydrate intake - also increase circulating BOHB levels. Ketogenic diets in animals elicit many of the biochemical changes associated with cellular protection from oxidative stress and with increased lifespan.

Canagliflozin treatment of diabetic patients, by inhibiting renal SGLT2 activity, induces glucosuria, which leads to increased utilization of stored fat reserves (resulting in reduced adiposity and body weight loss). Like fasting and ketogenic diets, canagliflozin treatment of diabetic patients also induces an increase in circulating ketone body levels, including BOHB.

There remains a need to provide an effective treatment for obesity and obesity related disorders (including disorders, diseases and conditions that are a result of, that are exacerbated by and / or that are hastened by obesity).

SUMMARY OF THE INVENTION

The present invention is directed to methods for treating, delaying, slowing the progression of and / or preventing obesity and obesity related disorders comprising administering to a subject in need thereof, a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is directed to a method for treating obesity, for promoting weight loss and / or for suppressing appetite comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising:

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is directed to a method for decreasing food intake, inducing satiety or controlling weight gain, comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising:

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

In certain embodiments, the present invention is directed to a method for chronic weight management, comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising:

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

In certain embodiments, the present invention is directed to methods for treating obesity, for promoting weight loss, for suppressing appetite, for decreasing food intake, for inducing satiety and / or for controlling weight gain, comprising identifying a subject in need thereof by determining the body mass index (BMI) of said subject; and wherein the body mass index of said subject is greater than or equal to about 25 kg/m^2 (preferably greater than or equal to about 30 kg/m^2), administering a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to a method of weight loss, a method of treating obesity, or a method of treating an obesity related disorder, comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

and wherein the amount of weight loss achieved after 26 weeks is about 5%, preferably about 7.5%, more preferably.

In an embodiment, the present invention is directed to a method of weight loss, a method of treating obesity, or a method of treating an obesity related disorder comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising canagliflozin and phentermine, as described herein, wherein the subject achieves or experiences a weight loss in the range of from about 5% to about 10%, or any amount or

range therein, preferably a weight loss of at least about 5%, more preferably, a weight loss of at least about 7.5%, within about 26 Weeks.

In another embodiment, the present invention is directed to a method of weight loss, a method of treating obesity, or a method of treating an obesity related disorder comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising canagliflozin and phentermine, as described herein, wherein the subject achieves or experiences a weight loss in the range of from about 5% to about 10%, or any amount or range therein, preferably a weight loss of at least about 5%, more preferably, a weight loss of at least about 7.5%, within a time period of between about 26 weeks and about 104 weeks, preferably within a time period of about 26 weeks and about 52 weeks.

In another embodiment, the present invention is directed to a method of weight loss, a method of treating obesity, or a method of treating an obesity related disorder comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising canagliflozin and phentermine, as described herein, wherein the co-therapy is administered in conjunction with diet and exercise counseling. In another embodiment, the present invention is directed to a method of weight loss, a method of treating obesity, or a method of treating an obesity related disorder comprising administering to a subject in need thereof co-therapy comprising canagliflozin and phentermine, as described herein, wherein the co-therapy is administered in conjunction with a diet and exercise program. In certain embodiments of the present invention, diet and exercise counseling or diet and exercise program comprises (a) advising the subject to increase physical activity, (b) advising the subject to reduce dietary fat content and / or (c) advising the subject to consume fewer calories. In certain embodiments, the present invention is directed to a method for chronic weight management comprising administering to a subject in need thereof co-therapy comprising canagliflozin and phentermine, as described herein, preferably wherein the co-therapy is an adjunct to a reduced-calorie diet and increased physical activity.

In certain embodiments of the present invention, a subject in need thereof is a subject (an adult or child) whose determined (e.g. measured) body mass index (BMI) is greater than or equal to about 23 kg/m^2. In certain additional embodiments of the present invention, a subject in need thereof is a subject (an adult or child) whose determined (e.g. measured) body mass index is greater than or equal to about 25 kg/m^2. In certain additional embodiments of the present invention, a subject in need thereof is a subject (an adult or child) whose determined (e.g. measured) body mass index is greater than or equal to about 30 kg/m^2. In certain additional embodiments of the present invention, a subject in need thereof is a subject (an adult or child) whose determined (e.g. measured) body mass index is greater than or equal to about 35 kg/m^2. In certain additional embodiments of the present invention, a subject in need thereof is a subject (an adult or child) whose determined (e.g. measured) body mass index is in the range of from about 23 kg/m^2 to about 29.9 kg/m^2.

In certain embodiments of the present invention, a subject in need thereof is a subject (an adult or child) whose determined (e.g. measured) body mass index is greater than or equal to about 23 kg/m^2, preferably greater than or equal to about 25 kg/m^2, more preferably greater than or equal to about 30 kg/m^2, more preferably greater than or equal to about 40 kg/m^2 and which subject is diagnosed with or exhibits at least one symptom of a co-morbid condition selected from the group consisting of pre-diabetes, impaired oral glucose tolerance, Type II diabetes mellitus, Metabolic syndrome (also known as Syndrome X), cardiovascular risk factors, a renal or fatty liver disorder (including but not limited to NASH, NAFLD, and the like), sleep apnea, and the like. In another embodiment, the co-morbid condition is selected from the group consisting of pre-diabetes, impaired oral glucose tolerance, Type II diabetes mellitus and Metabolic Syndrome (also known as Syndrome X). In another embodiment, the co-morbid condition is selected from the group consisting cardiovascular risk factors and a renal or fatty liver disorder (including but not limited to NASH, NAFLD, and the like).

In certain embodiments of the present invention, a subject in need thereof is a subject with an initial body mass index greater than or equal to about 30 kg/m^2; or greater than or equal to about 27 kg/m^2 and diagnosed with or exhibits

at least one weight-related co-morbid condition (such as, e.g., hypertension, dyslipidemia, pre-diabetes, or Type II diabetes mellitus).

In certain embodiments of the present invention, a subject in need thereof is a subject whose waist-to-hip ratio is greater than or equal to 1.0 if the subject is a male or is greater than or equal to about 0.8 if the subject is a female. In certain additional embodiments of the present invention, a subject in need thereof is a subject whose waist circumference is >40 inches or 102 cm if the subject is a male or is >35 inches or 94 cm if the subject is a female.

In certain embodiments of the present invention, a subject in need thereof is a subject whose body fat content is greater than about 25%, preferably greater than about 30%. In certain additional embodiments, a subject in need thereof is a subject whose body fat content is greater than about 25% is the subject is a male or greater than about 30% if the subject is female.

In certain embodiments, the present invention is directed to methods for treating obesity, promoting weight loss, suppressing appetite, decreasing food intake, inducing satiety and / or controlling weight gain, in a subject in need thereof, wherein the subject in need thereof is a candidate for or has had bariatric surgery (including gastric bypass surgery, gastric / stomach band surgery, and the like).

In certain embodiments, the present invention is directed to methods for treating obesity, promoting weight loss, suppressing appetite, decreasing food intake, inducing satiety and / or controlling weight gain, in a subject in need thereof, wherein the subject in need thereof is a candidate for or has had implanted a weight loss promoting medical device (for example, an endoluminal sleeve, an intragastric balloon, a device that reduces or reallocates the volume of a subject's gastrointestinal lumen, a device which delivers an electrical current to stimulate the stomach or other nerves of the digestive tract, a device which delivers electrical charges to inhibit the vagus nerve leading to the stomach, a deep-brain stimulation device, a device that delivers an electrical charge to parts of the nervous system that are activated by exercise, and the like).

In an embodiment, the present invention is directed to a method of treating obesity comprising administering to a subject in need thereof a therapeutically effective amount of any the co-therapy as herein described. In another embodiment, the present invention is directed to a method of promoting weight loss comprising administering to a subject in need thereof a therapeutically effective amount of the co-therapy as herein described. In another embodiment, the present invention is directed to a method of suppressing appetite comprising administering to a subject in need thereof a therapeutically effective amount of the co-therapy as herein described. In another embodiment, the present invention is directed to a method of decreasing food intake comprising administering to a subject in need thereof a therapeutically effective amount of the co-therapy as herein described. In another embodiment, the present invention is directed to a method of inducing satiety comprising administering to a subject in need thereof a therapeutically effective amount of the co-therapy as herein described. In another embodiment, the present invention is directed to a method of controlling weight gain comprising administering to a subject in need thereof a therapeutically effective amount of the co-therapy as herein described.

In an embodiment, the present invention is directed to methods for treating obesity, for promoting weight loss, for suppressing appetite, for decreasing food intake, for inducing satiety and / or for controlling weight gain, wherein the subject in need thereof has a measure BMI of greater than about 25 kg/m^2 and who has one or more concomitant (or co-existing) conditions selected from the group consisting of pre-diabetes, impaired oral glucose tolerance, Type II diabetes mellitus, Metabolic syndrome (also known as Syndrome X), cardiovascular risk factors, a renal or fatty liver disorder (including but not limited to NASH, NAFLD, and the like) and sleep apnea.

In another embodiment, the present invention is directed to methods for treating of obesity, promoting weight loss, suppressing appetite, decreasing food intake, inducing satiety and / or controlling weight loss wherein the subject in need thereof has a measure BMI of greater than about 25 kg/m^2 and who has one or more concomitant (or co-existing) conditions selected from the

group consisting of pre-diabetes, impaired oral glucose tolerance, Type II diabetes mellitus and Metabolic syndrome (also known as Syndrome X). In another embodiment, the present invention is directed to methods for treating of obesity, promoting weight loss, suppressing appetite, decreasing food intake, inducing satiety and / or controlling weight loss wherein the subject in need thereof has a measure BMI of greater than about 25 kg/m^2 and who has one or more concomitant (or co-existing) conditions selected from the group consisting cardiovascular risk factors and a renal or fatty liver disorder (including but not limited to NASH, NAFLD, and the like).

The present invention is further directed to methods for treating, delaying, slowing the progression and / or preventing a metabolic disorder (including, but not limited to hyperglycemia, pre-diabetes, impaired oral glucose tolerance, impaired fasting blood glucose, postprandial hyperglycemia, hyperinsulinemia, insulin resistance, Type 2 diabetes mellitus (including, but not limited to late stage Type 2 diabetes mellitus), Type 1 diabetes, MODY, LADA, NODAT, gestational diabetes, insufficient glycemic control (or inadequate glycemic control) and Metabolic Syndrome (also known as Syndrome X)), comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

In an embodiment of the present invention, the metabolic disorder is selected from the group consisting of pre-diabetes, impaired oral glucose tolerance, impaired fasting blood glucose, insulin resistance, Type 2 diabetes

mellitus and Syndrome X. In another embodiment of the present invention, the metabolic disorder is selected from the group consisting of Type 1 diabetes mellitus, Type 2 diabetes mellitus, maturity onset diabetes of the youth (MODY), latent autoimmune diabetes of adults (LADA) and pre-diabetes.

In an embodiment of the present invention, the subject in need thereof has been diagnosed with or shows symptoms of one or more of the following conditions Type 1 diabetes mellitus, Type 2 diabetes mellitus, maturity onset diabetes of the youth (MODY), latent autoimmune diabetes of adults (LADA) or pre-diabetes. In another embodiment of the present invention, the subject in need thereof has been diagnosed with or shows symptoms of Type 2 diabetes mellitus and/or diabetic nephropathy. In another embodiment of the present invention, the subject in need thereof has been diagnosed with or shows symptoms of Type 2 diabetes mellitus and/or insufficient glycemic control.

In another embodiment of the present invention, the subject in need thereof is:

(1) an individual diagnosed of one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

(2) an individual who shows one, two or more of the following signs:

(a) a fasting blood glucose or serum glucose concentration greater than about 100 mg/dL, in particular greater than about 125 mg/dL;

(b) a postprandial plasma glucose equal to or greater than about 140 mg/dL;

(c) an HbA1c value equal to or greater than about 7.0%;

(3) an individual wherein one, two, three or more of the following conditions are present:

(a) obesity, visceral obesity and/or abdominal obesity,

(b) triglyceride blood level equal to or greater than about 150 mg/dL,

(c) HDL-cholesterol blood level less than about 40 mg/dL in female patients and less than about 50 mg/dL in male patients,

(d) a systolic blood pressure equal to or greater than about 130 mm Hg and a diastolic blood pressure equal to or greater than about 85 mm Hg,

(e) a fasting blood glucose level equal to or greater than about 100 mg/dL; or

(4) an individual with obesity.

In an embodiment, the present invention is directed to methods for preventing, slowing the development or slowing the progression of Type 2 diabetes mellitus comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods of providing cardiovascular protection comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for preventing a major adverse cardiac event (MACE) (for example, myocardial infarction, unstable angina, cardiovascular death, revascularization, fatal or non-fatal cerebrovascular accident, peripheral arteriopathy, aortic events, hospitalization due to congestive heart failure) comprising administering to a subject in need thereof, a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for treating, delaying, slowing the progression of and / or preventing a cardiovascular event (including major adverse cardiac events (MACE) such as myocardial infarction, unstable angina, cardiovascular death, revascularization, fatal or non-fatal cerebrovascular accident, peripheral arteriopathy, aortic events, hospitalization due to congestive heart failure, and the like); comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of 100 mg or about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an

amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

In an embodiment of the present invention the MACE or cardiovascular event is selected from the group consisting of myocardial infarction, unstable angina, cardiovascular death, revascularization, fatal or non-fatal cerebrovascular accident (e.g. stroke), peripheral arteriopathy, aortic event and hospitalization due to congestive heart failure. In another embodiment of the present invention, the cardiovascular event is selected from the group consisting of myocardial infarction, fatal or non-fatal cerebrovascular accident (e.g. stroke) or hospitalization due to congestive heart failure. In another embodiment of the present invention the MACE or cardiovascular event is myocardial infarction or fatal or non-fatal cerebrovascular event (e.g. stroke). In another embodiment of the present invention the MACE or cardiovascular event is fatal or non-fatal cerebrovascular event (e.g. stroke). In another embodiment of the present invention the MACE or cardiovascular event is myocardial infarction.

In an embodiment, the present invention is directed to methods for decreasing blood pressure, preferably decreasing systolic blood pressure, comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for treating, delaying, slowing the progression of and / or preventing a renal or fatty liver disorder (including, but not limited to NASH, NAFLD, and the like) comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

In an embodiment of the present invention, the renal or fatty liver disorder is selected from the group consisting of alcoholic simple fatty liver, alcoholic steatohepatitis (ASH), alcoholic hepatic fibrosis, alcoholic cirrhosis, nonalcoholic fatty liver disease (NAFLD), nonalcoholic simple fatty liver, nonalcoholic steatohapatitis (NASH), nonalcoholic hepatic fibrosis, and nonalcoholic cirrhosis. In another embodiment of the present invention, the renal or fatty liver disorder is selected from the group consisting of nonalcoholic fatty liver disease (NAFLD), nonalcoholic simple fatty liver, nonalcoholic steatohapatitis (NASH), nonalcoholic hepatic fibrosis, and nonalcoholic cirrhosis. In another embodiment of the present invention, the renal or fatty liver disorder is selected from the group consisting of NAFLD and NASH. In another embodiment of the present invention, the renal disorder is diabetic nephropathy.

In another embodiment of the present invention, the renal or fatty liver disorder is selected from the group consisting of hyperfiltrative diabetic nephropathy, renal hyperfiltration, glomerular hyperfiltration, renal allograft hyperfiltration, compensatory hyperfiltration, hyperfiltrative chronic kidney disease and hyperfiltrative acute renal failure. In another embodiment of the

present invention, the renal disorder is selected from the group consisting of microalbuminuria, macroalbuminuria, elevated urine albumin levels and elevated albumin/creatinine ratio (ACR).

The present invention is further directed to methods for (a) treating, delaying, slowing the progression of, inducing remission of or preventing microalbuminuria (elevated urine albumin levels); (b) treating, delaying, slowing the progression of, or preventing macroalbuminuria; (c) decreasing urine albumin levels; and/or (d) decreasing albumin/creatinine ratio (ACR); comprising administering to subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for preventing, slowing the progression of, delaying and / or treating renal hyperfiltrative injury comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an

amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for preventing, slowing the progression of, delaying or treating a condition or disorder selected from the group consisting of hyperfiltrative diabetic nephropathy, renal hyperfiltration, glomerular hyperfiltration, renal allograft hyperfiltration, compensatory hyperfiltration (e.g. after renal mass reduction by surgery), hyperfiltrative chronic kidney disease, hyperfiltrative acute renal failure, and obesity comprising administering to a subject in need thereof, co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for treating, delaying, slowing the progression of and / or preventing diabetic neuropathy comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an

amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

In an embodiment of the present invention, the subject in need thereof has been diagnosed with or shows symptoms of one or more of the following conditions:

(a) diabetes mellitus, regardless of type;

(b) chronic kidney disease (CKD);

(c) acute renal failure (ARF);

(d) renal transplant recipients;

(e) renal transplant donors; or

(f) unilateral total or partial nephrectomized patients; or

(g) nephrotic syndrome.

The present invention is further directed to methods for treating or preventing a sleep disorder (including, but not limited to sleep apnea, and the like) comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for prolonging the life or life span of a subject, comprising administering to the subject co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an

amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

The present invention is further directed to methods for treating obesity, for promoting weight loss, for suppressing appetite, for decreasing food intake, for inducing satiety and / or for controlling weight gain, comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

wherein the subject in need thereof is a subject who is taking one or more pharmaceutical agents (drugs) whose potential side effect(s) include weight gain.

The present invention is further directed to methods of treating, delaying, slowing the progression of and / or preventing a disorder selected from the group consisting of shortness of breath, gallbladder disease, cancer (e.g. endometrial, breast, prostate, colon), osteoarthritis, orthopedic problems, reflux esophagitis (heartburn), snoring, polycystic ovary syndrome, stress incontinence, menstrual irregularities, infertility, heart trouble, depression, anxiety, gout, beta-cell dysfunction, hypopnea, comprising administering to a

subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 100 mg to about 300 mg, more preferably in an amount of about 100 mg or an amount of about 300 mg); and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 3.75 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 7.5 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 15 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 30 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 37.5 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 3.75 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 7.5 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin;

wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 15 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 30 mg per day.

In an embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is administered in an amount of about 37.5 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 3.75 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b)

phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 7.5 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 15 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 30 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 100 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 37.5 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the

canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 3.75 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 7.5 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 15 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 30 mg per day.

In another embodiment, the present invention is directed to methods of treating, delaying, slowing the progression of or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin; wherein the canagliflozin is a crystalline hemihydrate; and wherein the

canagliflozin is administered in an amount of about 300 mg per day; and (b) phentermine; wherein the phentermine is phentermine hydrochloride and wherein the phentermine is administered in an amount of about 37.5 mg per day.

In certain embodiments of the present invention, the canagliflozin is a crystalline, hemihydrate canagliflozin. In certain embodiments of the present invention, the phentermine is phentermine hydrochloride.

In an embodiment of the present invention, canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg. In another embodiment of the present invention, canagliflozin is administered in an amount in the range of from about 100 mg to about 300 mg. In another embodiment of the present invention, canagliflozin is administered in an amount of about 100 mg. In another embodiment of the present invention, canagliflozin is administered in an amount of about 300 mg.

In an embodiment of the present invention, phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg. In another embodiment of the present invention, phentermine is administered in an amount in the range of from about 3.75 mg to about 37.5 mg. In another embodiment of the present invention, phentermine is administered in an amount in the range of from about 7.5 mg to about 37.5 mg. In another embodiment of the present invention, phentermine is administered in an amount in the range of from about 7.5 mg to about 15 mg. In another embodiment of the present invention, phentermine is administered in an amount of about 3.75 mg. In another embodiment of the present invention, phentermine is administered in an amount of about 7.5 mg. In another embodiment of the present invention, phentermine is administered in an amount of about 15 mg. In another embodiment of the present invention, phentermine is administered in an amount of about 30 mg. In another embodiment of the present invention, phentermine is administered in an amount of about 37.5 mg.

In another embodiment of the present invention, phentermine is administered in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg or about 37.5 mg. In another embodiment of the present invention, phentermine is administered in an amount of about 3.75 mg, about 7.5 mg or about 15 mg. In another embodiment of the present invention, phentermine is administered in an amount of about 7.5 mg or about 15 mg.

In an embodiment, the co-therapy comprises canagliflozin in an amount of about 100 mg and phentermine in an amount of about 3.75 mg, administered at least once daily (preferably once daily). In another embodiment, the co-therapy comprises canagliflozin in an amount of about 100 mg and phentermine in an amount of about 7.5 mg, administered at least once daily (preferably once daily). In an embodiment, the co-therapy comprises canagliflozin in an amount of about 100 mg and phentermine in an amount of about 15 mg, administered at least once daily (preferably once daily). In an embodiment, the co-therapy comprises canagliflozin in an amount of about 100 mg and phentermine in an amount of about 30 mg, administered at least once daily (preferably once daily). In an embodiment, the co-therapy comprises canagliflozin in an amount of about 100 mg and phentermine in an amount of about 37.5 mg, administered at least once daily (preferably once daily).

In an embodiment, the co-therapy comprises canagliflozin in an amount of about 300 mg and phentermine in an amount of about 3.75 mg, administered at least once daily (preferably once daily). In another embodiment, the co-therapy comprises canagliflozin in an amount of about 300 mg and phentermine in an amount of about 7.5 mg, administered at least once daily (preferably once daily). In an embodiment, the co-therapy comprises canagliflozin in an amount of about 300 mg and phentermine in an amount of about 15 mg, administered at least once daily (preferably once daily). In an embodiment, the co-therapy comprises canagliflozin in an amount of about 300 mg and phentermine in an amount of about 30 mg, administered at least once daily (preferably once daily). In an embodiment, the co-therapy comprises canagliflozin in an amount of about 300 mg and phentermine in an amount of about 37.5 mg, administered at least once daily (preferably once daily).

Illustrative of the invention is a pharmaceutical composition comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 50 mg to about 300 mg, more preferably in an amount of about 50 mg, about 100 mg or about 300 mg); (b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 mg to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg or about 37.5 mg); and (c) a pharmaceutically acceptable carrier.

An illustration of the invention is a pharmaceutical composition made by mixing (a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 50 mg to about 300 mg, more preferably in an amount of about 50 mg, about 100 mg, or about 300 mg); (b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 mg to about 37.5 mg, more preferably in an amount of about 37.5 mg, about 7.5 mg, about 15 mg, about 30 mg or about 37.5 mg); and (c) a pharmaceutically acceptable carrier. Illustrating the invention is a process for making a pharmaceutical composition comprising mixing the product prepared according to the process described herein and a pharmaceutically acceptable carrier.

Exemplifying the invention are methods for treating, delaying, slowing the progression of and / or preventing obesity and obesity related disorders comprising administering to a subject in need thereof a therapeutically effective amount of any of the pharmaceutical compositions described herein.

In another embodiment, the present invention is directed to a composition comprising (a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from 50 mg to about 300 mg, more preferably in an amount of about 50 mg, about 100 mg or about 300 mg);

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 37.5 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 mg to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg or about 37.5 mg); and (c) a pharmaceutically acceptable carrier; for treating, delaying, slowing the progression of and / or preventing obesity and obesity related disorders.

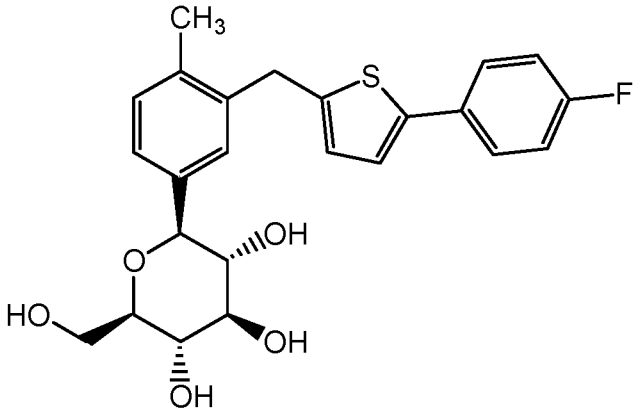
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to methods for treating, delaying, slowing the progression of and / or preventing obesity and obesity related disorders (including metabolic disorders such as pre-diabetes, Type 2 diabetes mellitus, Syndrome X, and the like, renal or fatty liver disorders such as NASH, NAFLD, and the like, cardiovascular events (or MACE), sleep apnea, etc.) comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin (preferably the crystalline hemihydrate form of canagliflozin); wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day (preferably in an amount in the range of from about 50 mg to about 300 mg, more preferably in an amount of about 50 mg, about 100 mg or about 300 mg); and

(b) phentermine (preferably phentermine hydrochloride); wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day (preferably in an amount in the range of from about 3.75 to about 37.5 mg, more preferably in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg, or about 37.5 mg).

As used herein, unless otherwise noted, the term “canagliflozin” shall mean a compound of formula (I-X);



(I-X)

also known as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol, or a crystalline, hemihydrate form of the compound of formula (I-X). The compound of formula (I-X) exhibits inhibitory activity against sodium-dependent glucose transporter, such as for example SGLT2; and may be prepared according to the process as disclosed in Nomura, S. et al., US Patent Publication, US 2005/0233988 A1, published October 20, 2005, which is incorporated by reference herein.

As used herein, the term "canagliflozin" shall further include a mixture of stereoisomers, or each pure or substantially pure isomer. In addition, the term "canagliflozin" shall include an intramolecular salt, hydrate, solvate or polymorph thereof. In certain embodiments, the term "canagliflozin" shall mean the crystalline hemihydrate form of the compound of formula (I-X), as described in WO 2008/069327, the disclosure of which is hereby incorporated by reference in its entirety.

As used herein, the term "phentermine" shall mean 2-methyl-1-phenylpropan-2-amine and pharmaceutically acceptable salts thereof, preferably phentermine hydrochloride. Phentermine is a sympathomimetic amine anorectic indicated as short-term adjunct in a regimen of weight loss reduction (including exercise, behavioral modification and caloric restriction) in the management of obesity. Phentermine is approved as an appetite suppressant and is medically prescribed as a diet pill; intended for obese patients and patients that are considered a medical risk due to weight. There are various phentermine brands and supplements available through tablets, capsules, and drinks including, VITES, ADIPED, ADIPEX-P, SUPRENZA,

IONAMIN and QSYMIA (a co-therapy with topiramate) available in various dosages, including the 15 mg, 30 mg and 37.5 mg.

In certain preferred embodiments, the dosage of phentermine (in mg) shall mean the amount of phentermine free base or free base equivalent (when the phentermine is present as a pharmaceutically acceptable salt thereof, for example as phentermine hydrochloride) that is administered or present in the pharmaceutical composition.

The term "body mass index" or "BMI" of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units of kg/m^2. The term "overweight" is defined as the condition wherein the adult individual of Europid origin has a BMI equal to or greater than 25 kg/m^2 and less than 30 kg/m^2. In subjects of Asian origin the term "overweight" is defined as the condition wherein the adult individual has a BMI equal to or greater than 23 kg/m^2 and less than 25 kg/m^2. The terms "overweight" and "pre-obese" are used interchangeably.

The term "obesity" is defined as the condition wherein the adult individual of Europid origin has a BMI equal to or greater than 30 kg/m^2. According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater than 30 kg/m^2 but lower than 35 kg/m^2; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 35 kg/m^2 but lower than 40 kg/m^2; the terms "class III obesity" is the condition wherein the BMI is equal to or greater than 40 kg/m^2. In subjects of Asian origin the term "obesity" is defined as the condition wherein the adult individual has a BMI equal or greater than 25 kg/m^2. Obesity in Asians may be categorized further as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater than 25 kg/m^2 but lower than 30 kg/m^2; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 30 kg/m^2.

The term "visceral obesity" is defined as the condition wherein a waist-to-hip ratio of greater than or equal to 1.0 in men and 0.8 in women is measured. It defines the risk for insulin resistance and the development of pre-diabetes. The term "abdominal obesity" is usually defined as the condition

wherein the waist circumference is >40 inches or 102 cm in men, and is >35 inches or 94 cm in women (for normal ranges of populations, see for example "Joint scientific statement (IDF, NHLBI, AHA, WHO, IAS, IASO). Circulation 2009; 120:1640-1645").

The term "morbid obesity" is defined herein as a condition in which the individual of Europid origin has a BMI >40 or has a BMI >35 and a comorbidity such as diabetes mellitus or hypertension (see World Health Organization. Obesity: Preventing and Managing the Global Epidemic: Report on a WHO Consultation. *World Health Organ Tech Rep Ser*. 2000; 894: i-xii, 1-253).

The term "euglycemia" is defined as the condition in which a subject has a fasting blood glucose concentration within the normal range, greater than 70 mg/dL (3.89 mmol/L) and less than 100 mg/dL (5.6 mmol/L), and a 2 h postprandial glucose concentration less than 140 mg/dl.

The term "hyperglycemia" is defined as the condition in which a subject has a fasting blood glucose concentration above the normal range, greater than 100 mg/dL (5.6 mmol/L).

The term "hypoglycemia" is defined as the condition in which a subject has a blood glucose concentration below the normal range, in particular below 70 mg/dL (3.89 mmol/L).

The term "postprandial hyperglycemia" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 200 mg/dL (11.11 mmol/L).

The term "impaired fasting blood glucose" or "IFG" is defined as the condition in which a subject has a fasting blood glucose concentration or fasting serum glucose concentration in a range from 100 to 125 mg/dl (i.e. from 5.6 to 6.9 mmol/l. A subject with "normal fasting glucose" has a fasting glucose concentration smaller than 100 mg/dl, i.e. smaller than 5.6 mmol/l.

The term "impaired glucose tolerance" or "IGT" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 140 mg/dl (7.78 mmol/L) and less than 200 mg/dL (11.11 mmol/L). The abnormal glucose tolerance, i.e. the 2 hour postprandial blood glucose or serum glucose concentration can be measured

as the blood sugar level in mg of glucose per dL of plasma 2 hours after taking 75 g of glucose after a fast. A subject with "normal glucose tolerance" has a 2 hour postprandial blood glucose or serum glucose concentration smaller than 140 mg/dl (7.78 mmol/L).

The term "hyperinsulinemia" is defined as the condition in which a subject with insulin resistance, with or without euglycemia, has fasting or postprandial serum or plasma insulin concentration elevated above that of normal, lean individuals without insulin resistance, having a waist-to-hip ratio<1.0 (for men) or <0.8 (for women).

The term "insulin resistance" is defined as a state in which circulating insulin levels in excess of the normal response to a glucose load are required to maintain the euglycemic state (Ford E S, et al. *JAMA*. (2002) 287:356-9). A method of determining insulin resistance is the euglycaemic-hyperinsulinaemic clamp test. The ratio of insulin to glucose is determined within the scope of a combined insulin-glucose infusion technique. There is found to be insulin resistance if the glucose absorption is below the 25th percentile of the background population investigated (WHO definition). Rather less laborious than the clamp test are so called minimal models in which, during an intravenous glucose tolerance test, the insulin and glucose concentrations in the blood are measured at fixed time intervals and from these the insulin resistance is calculated. With this method, it is not possible to distinguish between hepatic and peripheral insulin resistance.

As a rule, other parameters are used in everyday clinical practice to assess insulin resistance. Preferably, the patient's triglyceride concentration is used, for example, as increased triglyceride levels correlate significantly with the presence of insulin resistance.

Patients with a predisposition for the development of IGT or IFG or Type 2 diabetes are those having euglycemia with hyperinsulinemia and are by definition, insulin resistant. A typical patient with insulin resistance is usually overweight or obese. If insulin resistance can be detected, this is a particularly strong indication of the presence of pre-diabetes. Thus, it may be that in order to maintain glucose homoeostasis a person needs 2-3 times as much insulin as a healthy person, without this resulting in any clinical symptoms.

The term "pre-diabetes" is the condition wherein an individual is pre-disposed to the development of type 2 diabetes. Pre-diabetes extends the definition of impaired glucose tolerance to include individuals with a fasting blood glucose within the high normal range 100 mg/dL (J. B. Meigs, et al. Diabetes 2003; 52:1475-1484) and fasting hyperinsulinemia (elevated plasma insulin concentration). The scientific and medical basis for identifying pre-diabetes as a serious health threat is laid out in a Position Statement entitled "The Prevention or Delay of Type 2 Diabetes" issued jointly by the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Diseases (Diabetes Care 2002; 25:742-749). Individuals likely to have insulin resistance are those who have two or more of the following attributes: 1) overweight or obese, 2) high blood pressure, 3) hyperlipidemia, 4) one or more 1st degree relative with a diagnosis of IGT or IFG or type 2 diabetes.

The term "Type 2 diabetes" is defined as the condition in which a subject has a fasting (i.e., no caloric intake for 8 hours) blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L), when measured at minimum two independent occasions. The measurement of blood glucose values is a standard procedure in routine medical analysis. Type 2 diabetes is also defined as the condition in which a subject has HbA1c equal to, or greater than 6.5%, a two hour plasma glucose equal to, or greater than 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT) or a random glucose concentration equal to, or greater than 200 mg/dL (11.1 mmol/L) in conjunction with classic symptoms of hyperglycaemia or hyperglycaemic crisis. In the absence of unequicoval hyperglycaemia, as with most diagnostic tests, a test result diagnostic of diabetes should be repeated to rule out laboratory error. The assessment of HbA1c should be performed using a method certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. If a OGTT is carried out, the blood sugar level of a diabetic will be in excess of 200 mg of glucose per dL (11.1 mmol/l) of plasma 2 hours after 75 g of glucose have been taken on an empty stomach. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after a minimum of 8 hours, typically after 10-12 hours, of fasting

and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. In a healthy subject, the blood sugar level before taking the glucose will be between 60 and 110 mg per dL of plasma, less than 200 mg per dL 1 hour after taking the glucose and less than 140 mg per dL after 2 hours. If after 2 hours the value is between 140 and 200 mg, this is regarded as abnormal glucose tolerance.

The term "late stage Type 2 diabetes mellitus" includes patients with a long-standing duration of diabetes, secondary drug failure, indication for insulin therapy and potentially progression to micro- and macrovascular complications e.g. diabetic nephropathy, or coronary heart disease (CHD).

The term "Type 1 diabetes" is defined as the condition in which a subject has, in the presence of autoimmunity towards the pancreatic beta-cell (i.e. detection of circulating islet cell autoantibodies ["type 1A diabetes mellitus"], i.e., at least one of: GAD65 [glutamic acid decarboxylase-65], ICA [islet-cell cytoplasm], IA-2 [intracytoplasmatic domain of the tyrosine phosphatase-like protein IA-2], ZnT8 [zinc-transporter-8] or anti-insulin; or other signs of autoimmunity without the presence of typical circulating autoantibodies [type 1B diabetes], i.e. as detected through pancreatic biopsy or imaging), a fasting (i.e., no caloric intake for 8 hours) blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L). Type 1 diabetes is also defined as the condition in which a subject has, in the presence of autoimmunity towards the pancreatic beta-cell, HbA1c equal to, or greater than 6.5%, a two hour plasma glucose equal to, or greater than 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT) or a random glucose equal to, or greater than 200 mg/dL (11.1 mmol/L) in conjunction with classic symptoms of hyperglycaemia or hyperglycaemic crisis. In the absence of uneqicoval hyperglycaemia, as with most diagnostic tests, a test result diagnostic of diabetes should be repeated to rule out laboratory error. The measurement of blood glucose values is a standard procedure in routine medical analysis. The assessment of HbA1c should be performed using a method certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. If an OGTT is carried out, the blood sugar level of a diabetic will be in

excess of 200 mg of glucose per dL (11.1 mmol/l) of plasma 2 hours after 75 g of glucose have been taken on an empty stomach, in the presence of autoimmunity towards the pancreatic beta cell. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after a minimum of 8 hours, typically, 10-12 hours, of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. Typically a genetic predisposition is present (e.g. HLA, INS VNTR and PTPN22), but this is not always the case.

The term "MODY" ("maturity onset diabetes of the youth") describes a monogenic form for diabetes that, according to gene affects, is split into MODY variants, e.g., MODY 1,2.3.4 etc.

The term "LADA" ("latent autoimmune diabetes of adults") refers to patients that has a clinical diagnosis of Type 2 Diabetes Mellitus, but who is being detected to have autoimmunity towards the pancreatic beta cell.

The term "HbA1c" refers to the product of a non-enzymatic glycation of the haemoglobin B chain. Its determination is well known to one skilled in the art. In monitoring the treatment of diabetes mellitus the HbA1c value is of exceptional importance. As its production depends essentially on the blood sugar level and the life of the erythrocytes, the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar levels of the preceding 4-6 weeks. Diabetic patients whose HbA1c value is consistently well adjusted by intensive diabetes treatment (i.e. <6.5% of the total haemoglobin in the sample), are significantly better protected against diabetic microangiopathy. For example, metformin on its own achieves an average improvement in the HbA1c value in the diabetic of the order of 1.0-1.5%. This reduction of the HbA1C value is not sufficient in all diabetics to achieve the desired target range of <6.5% and preferably <6% HbA1c.

The term "insufficient glycemic control" or "inadequate glycemic control" in the scope of the present invention means a condition wherein patients show HbA1c values above 6.5%, in particular above 7.0%, even more preferably above 7.5%, especially above 8%.

The "metabolic syndrome", also called "syndrome X" (when used in the context of a metabolic disorder), also called the "dysmetabolic syndrome" is a

syndrome complex with the cardinal feature being insulin resistance (Laaksonen D E, et al. *Am J Epidemiol* 2002; 156:1070-7). According to the ATP III/NCEP guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) *JAMA: Journal of the American Medical Association* (2001) 285:2486-2497), diagnosis of the metabolic syndrome is made when three or more of the following risk factors are present:

1. Abdominal obesity, defined as waist circumference greater than about 40 inches or 102 cm in men, and greater than about 35 inches or 94 cm in women;
2. Triglycerides equal to or greater than about 150 mg/dL;
3. HDL-cholesterol less than about 40 mg/dL in men and less than about 50 in women;
4. Blood pressure equal to or greater than about 130/85 mm Hg (SBP equal to or greater than about 130 or DBP equal to or greater than about 85);
5. Fasting blood glucose equal to or greater than about 100 mg/dL.

According to a commonly used definition, hypertension is diagnosed if the systolic blood pressure (SBP) exceeds a value of 140 mm Hg and diastolic blood pressure (DBP) exceeds a value of 90 mm Hg. If a patient is suffering from manifest diabetes it is currently recommended that the systolic blood pressure be reduced to a level below 130 mm Hg and the diastolic blood pressure be lowered to below 80 mm Hg.

The definitions of NODAT (new onset diabetes after transplantation) and PTMS (post-transplant metabolic syndrome) follow closely that of the American Diabetes Association diagnostic criteria for type 2 diabetes, and that of the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute, for the metabolic syndrome. NODAT and/or PTMS are associated with an increased risk of micro- and macrovascular disease and events, graft rejection, infection, and death. A number of predictors have been identified as potential risk factors related to NODAT and/or PTMS including a higher age at transplant, male

gender, the pre-transplant body mass index, pre-transplant diabetes, and immunosuppression.

The term "gestational diabetes" (diabetes of pregnancy) denotes a form of the diabetes which develops during pregnancy and usually ceases again immediately after the birth. Gestational diabetes is diagnosed by a screening test which often is carried out between the 24th and 28th weeks of pregnancy, but could be conducted at any time during pregnancy, in particular if previous gestational diabetes has been diagnosed. It is usually a simple test in which the blood sugar level is measured e.g., one hour after the administration of 50 g of glucose solution. If this 1 h level is above 140 mg/dl, gestational diabetes is suspected. Final confirmation may be obtained by a standard glucose tolerance test, for example with 75 g of glucose; which also serve as a diagnostic test in the absence of the 50 g challenge.

As used herein, unless otherwise noted, the term "obesity related disorder" shall mean any disease, disorder or condition which is characterized by excess body weight or any disease, disorder or condition which is exacerbated, intensified or whose progression is accelerated as a result of excess weight. Also included is any disease, disorder or condition where at least on symptom or manifestation of said disease, disorder or condition is exacerbated, intensified or whose progression is accelerated as a result of excess weight. Suitably examples of obesity related disorders include, but are not limited to

(a) overweight or obesity;

(b) metabolic disorders such as pre-diabetes, impaired oral glucose tolerance, impaired fasting blood glucose, insulin resistance, Type 1 diabetes mellitus, Type 2 diabetes mellitus, maturity onset diabetes of the youth (MODY), latent autoimmune diabetes of adults (LADA), NODAT, gestational diabetes, hyperglycemia, post prandial hyperglycemia, hyperinsulinemia, insufficient glycemic control (or inadequate glycemic control) and Syndrom X (also known as Metabolic Syndrome), and the like;

(c) renal or fatty liver disorders (such as alcoholic simple fatty liver, alcoholic steatohepatitis (ASH), alcoholic hepatic fibrosis, alcoholic cirrhosis, nonalcoholic fatty liver disease (NAFLD), nonalcoholic simple fatty liver,

nonalcoholic steatohapatitis (NASH), nonalcoholic hepatic fibrosis, and nonalcoholic cirrhosis, hyperfiltrative diabetic nephropathy, renal hyperfiltration, glomerular hyperfiltration, renal allograft hyperfiltration, compensatory hyperfiltration, hyperfiltrative chronic kidney disease, hyperfiltrative acute renal failure, microalbuminuria (elevated urine albumin levels), macroalbuminuria, elevated urine albumin levels, elevated albumin/creatinine ratio (ACR), chronic kidney disease (CKD), acute renal failure (ARF), and the like;

(d) MACE or cardiovascular events (such as myocardial infarction, unstable angina, cardiovascular death, revascularization, fatal/nonfatal cerebrovascular accident, peripheral arteriopathy, aortic event, hospitalization due to congestive heart failure, and the like);

and (e) sleep disorders (such as sleep apnea, and the like).

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

In certain embodiments of the present invention, the subject is overweight or obese. In additional embodiments of the present invention, the subject is overweight or obese and has been diagnosed with or exhibits at least one symptom of an obesity related disorder. In additional embodiments of the present invention, the subject is has a measured or determined BMI is greater than or equal to about 25 kg/m^2, preferably greater than or equal to about 30 kg/m^2.

In certain embodiments of the present invention, the subject is diabetic. In certain embodiments of the present invention, the subject is pre-diabetic. In certain embodiments of the present invention, the subject is non-diabetic.

As used herein, unless otherwise noted, the terms "treating", "treatment" and the like, shall include the management and care of a subject or patient (preferably a mammal, more preferably a human) for the purpose of combating a disease, condition, or disorder. The terms "treating" and "treatment" include the administration of the compound(s) or pharmaceutical composition(s) as described herein to (a) alleviate one or more symptoms or complications of the disease, condition or disorder; (b) prevent the onset of one or more symptoms

or complications of the disease, condition or disorder; and / or (c) eliminate one or more symptoms or complications of the disease, condition, or disorder.

As used herein, unless otherwise noted, the terms "delaying the progression of" and "slowing the progression of" shall include (a) delaying or slowing the development of one or more symptoms or complications of the disease, condition or disorder; (b) delaying or slowing the development of one or more new / additional symptoms or complications of the disease, condition or disorder; and / or (c) delaying or slowing the progression of the disease, condition or disorder to a later stage or more serious form of said disease, condition or disorder.

As used herein, unless otherwise noted, the terms "preventing" and "prevention" shall include (a) reducing the frequency of one or more symptoms; (b) reducing the severity of one or more symptoms; (c) delaying, slowing or avoiding of the development of one or more additional symptoms; and / or (d) delaying, slowing or avoiding the development of the disorder, condition or disease to a later stage or more serious form.

One skilled in the art will recognize that wherein the present invention is directed to methods of prevention, a subject in need of thereof (i.e. a subject in need of prevention) shall include any subject or patient (preferably a mammal, more preferably a human) who has experienced or exhibited at least one symptom of the disorder, disease or condition to be prevented. Further, a subject in need thereof may additionally be a subject (preferably a mammal, more preferably a human) who has not exhibited any symptoms of the disorder, disease or condition to be prevented, but who has been deemed by a physician, clinician or other medical profession to be at risk of developing said disorder, disease or condition. For example, the subject may be deemed at risk of developing a disorder, disease or condition (and therefore in need of prevention or preventive treatment) as a consequence of the subject's medical history, including, but not limited to, family history, pre-disposition, co-existing (comorbid) disorders or conditions, genetic testing, and the like.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or

medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Wherein the present invention is directed to co-therapy or combination therapy, comprising administration of (a) canagliflozin and (b) phentermine "therapeutically effective amount" shall mean that amount of the combination of agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of co-therapy comprising administration of (a) canagliflozin and (b) phentermine would be the amount of (a) canagliflozin and the amount of (b) phentermine that when taken together or sequentially have a combined effect that is therapeutically effective. Further, it will be recognized by one skilled in the art that in the case of co-therapy or combination therapy with a therapeutically effective amount, as in the example above, the amount of (a) canagliflozin) and/or the amount of (b) phentermine individually may or may not be therapeutically effective.

As used herein, the terms "co-therapy" and "combination therapy" shall mean treatment of a subject in need thereof by administering (a) canagliflozin and (b) phentermine, wherein the (a) canagliflozin and (b) phentermine are administered by any suitable means, simultaneously, sequentially, separately or in a single pharmaceutical formulation (as long as the canagliflozin and phentermine are present in the subject, to some extent, at the same time). Where the (a) canagliflozin and (b) phentermine are administered in separate dosage forms, the number of dosages administered per day for each compound may be the same or different. The (a) canagliflozin and (b) phentermine may be administered via the same or different routes of administration. Examples of suitable methods of administration include, but are not limited to, oral, intravenous (iv), intramuscular (im), subcutaneous (sc), transdermal, and rectal. The (a) canagliflozin and (b) phentermine may also be administered directly to the nervous system including, but not limited to, intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal and / or peri-spinal routes of administration by delivery via intracranial or intravertebral needles and / or catheters with or without pump

devices. The (a) canagliflozin and (b) phentermine may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

The present invention is directed to combination therapy or co-therapy as described herein. Combination therapy or co-therapy is advantageous because in certain instances, the co-administration of active ingredients achieves a therapeutic effect that is greater than the therapeutic effect achieved by administration of only a single therapeutic agent.

In certain embodiments, the co-administration (combination therapy or co-therapy) of two or more therapeutic agents achieves a therapeutic effect that is greater than the therapeutic effect achieved by administration of only a single therapeutic agent. In this regard, the therapeutic effect of one therapeutic agent is augmented by the co-administration of another therapeutic agent. In certain embodiments, the co-administration of two or more therapeutic agents achieves a therapeutic effect that is equal to about the sum of the therapeutic effects achieved by administration of each single therapeutic agent. In these embodiments, the combination therapies are said to be “additive.” In certain embodiments, the co-administration of two or more therapeutic agents achieves a synergistic effect, i.e., a therapeutic effect that is greater than the sum of the therapeutic effects of the individual components of the combination.

In certain embodiments, the therapeutic agents are administered in a single dosage form, wherein each individual therapeutic agent is isolated from the other therapeutic agent(s). Formulating the dosage forms in such a way assists in maintaining the structural integrity of potentially reactive therapeutic agents until they are administered. A formulation of this type may be useful during production and for long term storage of the dosage form. In certain embodiments, the therapeutic agents may comprise segregated regions or distinct caplets or the like housed within a capsule. In certain embodiments, the therapeutic agents are provided in isolated layers comprised by a tablet.

Alternatively, the therapeutic agents may be administered as separate compositions, e.g., as separate tablets or solutions. One or more active agent may be administered at the same time as the other active agent(s) or the active

agents may be administered intermittently. The length of time between administrations of the therapeutic agents may be adjusted to achieve the desired therapeutic effect. In certain instances, one or more therapeutic agent(s) may be administered only a few minutes (e.g., about 1, 2, 5, 10, 30, or 60 min) after administration of the other therapeutic agent(s). Alternatively, one or more therapeutic agent(s) may be administered several hours (e.g., about 2, 4, 6, 10, 12, 24, or 36 hr) after administration of the other therapeutic agent(s). In certain embodiments, it may be advantageous to administer more than one dosage of one or more therapeutic agent(s) between administrations of the remaining therapeutic agent (s). For example, one therapeutic agent may be administered at 2 hours and then again at 10 hours following administration of the other therapeutic agent(s). Importantly, it is required that the therapeutic effects of each active ingredient overlap for at least a portion of the duration of each therapeutic agent so that the overall therapeutic effect of the combination therapy is attributable in part to the combined or synergistic effects of the combination therapy.

Since two or more different active agents are being used together in a combination therapy, the potency of each agent and the interactive effects achieved using them together must be considered. Importantly, the determination of dosage ranges and optimal dosages for a particular mammal is also well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure.

The term “synergistic” refers to a combination which is more effective than the additive effects of any two or more single agents. A synergistic effect permits the effective treatment of a disease, disorder or condition using lower amounts (doses) of individual therapy. The lower doses result in lower toxicity without reduced efficacy. In addition, a synergistic effect can result in improved efficacy. Finally, synergy may result in an improved avoidance or reduction of disease as compared to any single therapy.

Combination therapy can allow for the product of lower doses of the first therapeutic or the second therapeutic agent (referred to as “apparent one-way synergy” herein), or lower doses of both therapeutic agents (referred to as “two

way synergy" herein) than would normally be required when either drug is used alone. In certain embodiments, the synergism exhibited between one or more therapeutic agent(s) and the remaining therapeutic agent(s) is such that the dosage of one of the therapeutic agents would be sub-therapeutic if administered without the dosage of the other therapeutic agents.

The terms "augmentation" or "augment" refer to combinations where one of the compounds increases or enhances therapeutic effects of another compound or compounds administered to a patient. In some instances, augmentation can result in improving the efficacy, tolerability, or safety, or any combination thereof, of a particular therapy.

In certain embodiments, the present invention relates to a pharmaceutical composition comprising a therapeutically effective dose of one or more therapeutic agent(s) together with a dose of another therapeutic agent effective to augment the therapeutic effect of the one or more therapeutic agent(s). In other embodiments, the present invention relates to methods of augmenting the therapeutic effect in a patient of one or more therapeutic agent(s) by administering another therapeutic agent to the patient.

In certain embodiments, the invention is directed in part to synergistic combinations of one or more therapeutic agent(s) in an amount sufficient to render a therapeutic effect together with the remaining therapeutic agent(s). For example, in certain embodiments a therapeutic effect is attained which is at least about 2 (or at least about 4, 6, 8, or 10) times greater than that obtained with the dose of the one or more therapeutic agent(s) alone. In certain embodiments, the synergistic combination provides a therapeutic effect which is up to about 20, 30 or 40 times greater than that obtained with the dose of the one or more therapeutic agent(s) alone. In such embodiments, the synergistic combinations display what is referred to herein as an "apparent one-way synergy", meaning that the dose of the remaining therapeutic agent(s) synergistically potentiates the effect of the one or more therapeutic agent(s), but the dose of the one or more therapeutic agent(s) does not appear to significantly potentiate the effect of the remaining therapeutic agent(s).

In certain embodiments, the combination of active agents exhibits two-way synergism, meaning that the second therapeutic agent potentiates the

effect of the first therapeutic agent, and the first therapeutic agent potentiates the effect of the second therapeutic agent. Thus, other embodiments of the invention relate to combinations of a second therapeutic agent and a first therapeutic agent where the dose of each drug is reduced due to the synergism between the drugs, and the therapeutic effect derived from the combination of drugs in reduced doses is enhanced. The two-way synergism is not always readily apparent in actual dosages due to the potency ratio of the first therapeutic agent to the second therapeutic agent. For instance, two-way synergism can be difficult to detect when one therapeutic agent displays much greater therapeutic potency relative to the other therapeutic agent.

The synergistic effects of combination therapy may be evaluated by biological activity assays. For example, the therapeutic agents are mixed at molar ratios designed to give approximately equipotent therapeutic effects based on the EC_{9O} or EC_{50} values. Then, three different molar ratios are used for each combination to allow for variability in the estimates of relative potency. These molar ratios are maintained throughout the dilution series. The corresponding monotherapies are also evaluated in parallel to the combination treatments using the standard primary assay format. A comparison of the therapeutic effect of the combination treatment to the therapeutic effect of the monotherapy gives a measure of the synergistic effect. Further details on the design of combination analyses can be found in B E Korba (1996) Antiviral Res. 29:49. Analysis of synergism, additivity, or antagonism can be determined by analysis of the aforementioned data using the CalcuSyn™ program (Biosoft, Inc.). This program evaluates drug interactions by use of the Widely accepted method of Chou and Talalay combined with a statistically evaluation using the Monte Carlo statistical package. The data are displayed in several different formats including median-effect and dose-effects plots, isobolograms, and combination index [CI] plots with standard deviations. For the latter analysis, a CI greater than 1 .0 indicates antagonism and a CI less than 1 .0 indicates synergism.

Compositions of the invention present the opportunity for obtaining relief from moderate to severe cases of disease. Due to the synergistic or additive or augmented effects provided by the inventive combination of the first and

second therapeutic agent, it may be possible to use reduced dosages of each of therapeutic agent. By using lesser amounts of drugs, the side effects associated with each may be reduced in number and degree. Moreover, the inventive combinations avoid side effects to which some patients are particularly sensitive. The present invention provides pharmaceutically acceptable compositions which comprise a therapeutically effective amount of two or more of the compounds described herein, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail herein, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

For use in medicine, the salts of the compounds of this invention refer to non-toxic “pharmaceutically acceptable salts”. Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., 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. Thus, representative pharmaceutically acceptable salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate.

Representative acids and bases which may be used in the preparation of pharmaceutically acceptable salts include the following: acids including acetic acid, 2,2-dichloroactic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydrocy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucoronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hipuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinc acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitric acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebaic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid; and bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine,

ethylenediamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value. Further, to provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that wherein a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any amount or range therein.

Pharmaceutical Compositions

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The present invention further comprises pharmaceutical compositions containing (a) canagliflozin, and (b) phentermine and a pharmaceutically acceptable carrier. Pharmaceutical compositions containing (a) canagliflozin and (b) phentermine as the active ingredients can be prepared by intimately mixing the compound or compounds with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending upon the desired route of administration (e.g.,

oral, parenteral). Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations may also be coated with substances such as sugars or be enteric-coated so as to modulate major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives.

To prepare the pharmaceutical compositions of this invention, (a) canagliflozin and (b) phentermine as the active ingredients are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder,

injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.1 mg to about 1000 mg, or any amount or range therein, and may be given at a dosage of from about 0.01-200.0 mg/kg/day, preferably from about 0.05 to 100 mg/kg/day, more preferably from about 0.05-50 mg/kg/day, more preferably from about 0.05-25.0 mg/kg/day, more preferably from about 0.05-10.0 mg/kg/day, most preferably from about 0.5 to about 7.5 mg/kg/day, or any range therein. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these pre-formulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid pre-formulation composition is then subdivided into unit dosage forms of the type described above containing

from 0.1 to about 1000 mg, or any amount or range therein, of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

To prepare certain pharmaceutical compositions of the present invention, canagliflozin, as the active ingredient, and phentermine, as the active ingredient may each be intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral) and thereafter be separately combined together. To prepare further pharmaceutical compositions of the present invention, canagliflozin and phentermine, as the active ingredients, may be intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in The Handbook of

Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain, the disclosure of which is hereby incorporated by reference.

Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1-3, edited by Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1-2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc., the disclosures of which are hereby incorporated by reference.

In addition to pharmaceutical solutions for the treatment of obesity, a variety of medical devices have been developed for use in the treatment of obesity, and are being introduced into clinical practice. While many of these devices are still in clinical trials, researchers remain optimistic regarding their prospects as components of low-severity, high-efficacy treatments for obesity. Moreover, the importance of these devices is magnified by the fact that many severely obese patients are not ideal candidates for surgical intervention. Therefore, such devices promise to provide new treatment options for patients suffering from obesity and other metabolic conditions, and in some cases may offer valuable alternatives to more invasive surgical approaches.

Endoluminal sleeves are one example of a device developed for the treatment of obesity. The sleeve creates a physical barrier between ingested food and the intestinal wall, thereby changing the metabolic pathway by controlling how food moves through the digestive system. This mechanical bypass of the small intestine mimics the effects on a patient's metabolism of gastric bypass surgery, often resulting in profound weight loss and remission of type 2 diabetes. The device can be implanted and removed endoscopically (via the mouth), without the need for surgical intervention.

Intragastric balloons are a second example. An intragastric balloon is designed to occupy volume within the stomach such that a smaller volume of food results in a feeling of satiety. Intragastric balloons currently on the market

are not fixed in the stomach and, consequently, can lead to complications such as obstruction and mucosal erosion. To avoid these complications, the balloons are removed after a maximum of six months. One study found that the average excess weight loss was about 48.3% after one year. However, the patients reported occurrences of nausea and vomiting; and a smaller number of patients suffered from epigastric pain. Furthermore, balloon impaction occurred in about 0.6% of patients. A balloon which is fixed to the wall of the stomach could potentially improve the overall safety and efficacy of this approach, and allow longer-term implantation.

Devices have also been developed that reduce or reallocate the volume of a patient's gastrointestinal lumen. An example of such a device comprises an anchor that, once deployed, reduces a cross-sectional area within the GI track of a patient. A number of related devices in this class, such as staples, blind staples, bands, clips, tags, adhesives, and screws, have been used to reduce or reallocate the volume of a patient's stomach, specifically.

Another approach involves the use of electrical current to stimulate the stomach or certain nerves of the digestive tract. Medtronic (Minneapolis) has developed a battery-powered, stopwatch-size gastric pacemaker (similar to a cardiac pacemaker) that causes the stomach to contract, sending signals of satiety to the appetite center in the brain. The gastric pacemaker is implanted under the skin of the abdomen with electric wires placed on the wall of the stomach. Additionally, the electricity will modify eating behavior by regulating appetite signals. Moreover, the gastric pacemaker may also work to boost metabolism, which can lead to further weight loss.

An implant that uses electrical charges to inhibit the main nerve (vagus nerve) leading to the stomach has also been developed. In this case, the electrical charge may slow down digestion; for example, due to the stimulation the stomach would not register that presence of food and, therefore, would not initiate the digestive process. By down-regulating the activity of the vagus nerve, the technology simultaneously controls multiple major biological functions related to obesity, including food intake, hunger perception and digestion. Furthermore, the modulation is reversible, and the therapy can be adjusted and programmed to meet an individual patient's treatment needs.

Deep-brain-stimulation technology is also being developed as a possible treatment for obesity, which uses tiny electrodes implanted in specific areas of the brain to affect behavior, movement and other functions. Brain stimulation technology is currently approved in the United States to treat movement disorders, such as Parkinson's disease, and is being studied to treat obsessive compulsive disorder and severe depression.

Also being examined are devices that deliver an electrical charge to the same parts of the nervous system that are activated by exercise, which is known to be associated with increased metabolism. Such devices may be able to help people lose weight by boosting their metabolism.

The methods of the present invention may also be carried out using a pharmaceutical composition comprising (a) canagliflozin and (b) phentermine as defined herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may contain between about 0.1 mg and 1000 mg, or any amount or range therein, preferably about 2.5 to 500 mg, of each of the canagliflozin and phentermine, and may be constituted into any form suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

Advantageously, the (a) canagliflozin and (b) phentermine co-therapy of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the (a) canagliflozin and (b) phentermine of the co-therapy of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal

delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the (a) canagliflozin and (b) phentermine can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The co-therapy of the present invention, and the (a) canagliflozin and (b) phentermine which comprise said co-therapy may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment of depression is required.

The daily dosage of each of canagliflozin, phentermine and/ or the co-therapy comprising canagliflozin and phentermine may be varied over a wide range from 0.01 to 150 mg / kg per adult human per day. For oral administration, each of canagliflozin, phentermine and/ or the co-therapy comprising canagliflozin and phentermine may be preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 3.75, 5.0, 7.5, 10.0, 15.0, 25.0, 30.0, 37.5, 50.0, 100, 150, 200, 250, 300, 500 and 1000 milligrams of the active ingredient(s) for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the active ingredient(s) is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 1500 mg/kg of body weight per day. Preferably, the

range is from about 0.05 to about 100.0 mg/kg of body weight per day, more preferably, from about 0.05 mg/kg to about 50 mg/kg, more preferably, from about 0.05 to about 25.0 mg/kg of body weight per day. The active ingredient(s) may be administered on a regimen of 1 to 4 times per day, concurrently, sequentially, separately or in a single dosage form.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Example 1: Clinical Trial

Co-therapy with 300 mg Canagliflozin and 15 mg Phentermine

The safety and efficacy of combination treatment with 300 mg canagliflozin and 15 mg phentermine was investigated in a 26 week, randomized, double-blind, placebo-controlled, parallel group, multi-center study. (Complete study protocol filed and available as STUDY 28431754-OBE2002 on www.clinicaltrials.gov).

Trial Design:

The study began with a 4-week single blind placebo run-in period. After completing the run-in period 335 overweight or obese non-diabetic adult subjects who had a BMI ≥30 kg/m^2 and <50 kg/m^2 at screening; or BMI ≥27 kg/m^2 and <50 kg/m^2 at screening in the presence of a comorbidity/comorbidities of hypertension and/or dyslipidemia were randomly assigned in a 1:1:1:1 ratio to treatment with (A) canagliflozin 300 mg and phentermine 15 mg, (B) canagliflozin 300 mg, (C) phentermine 15 mg, or (D) placebo with the stratification factor: run-in weight loss of ≤2 kg or >2 kg. All

subjects were provided with diet and exercise counseling for weight loss (standardized non-pharmacological therapy) and were instructed to follow the diet and exercise program throughout the study.

The modified intent-to-treat (mITT) analysis set included all randomized subjects who had received at least one dose of study drug. The primary efficacy endpoint was percent change from baseline in body weight at Week 26. The secondary efficacy endpoints included (1) proportion of subjects with weight loss ≥5% at Week 26, (2) absolute change from baseline in SBP (static blood pressure) at Week 26, and (3) absolute change from baseline in body weight at Week 26. The inclusion of canagliflozin 300 mg and phentermine 15 mg as separate treatment groups allowed for a descriptive estimate of relative contribution of the individual components to the observed weight loss in the co-therapy canagliflozin 300 mg/phentermine 15 mg group and provided efficacy and safety data on canagliflozin 300 mg in the non-diabetic, overweight/obese population. Safety analyses included treatment-emergent adverse events (referred to as adverse events in this document), laboratory tests (including chemistry and hematology), and vital signs (blood pressure and pulse rate).

There were 335 subjects randomized and 334 subjects dosed; 334 subjects comprised the mITT analysis set of whom 231 (69%) completed the study. One subject was inadvertently randomized after not meeting eligibility criteria and was not dosed. The proportion of subjects who discontinued was lower in the co-administration of canagliflozin 300 mg and phentermine 15 group compared to the other treatment groups. Overall, lost to follow-up and adverse event were the most frequent reasons for discontinuation (12.9% and 7.5%, respectively). No subjects discontinued due to a serious adverse event (SAE).

The majority of subjects were female (81.7%), white (78.4%), mean age of 45.7 years, mean baseline HbA_{1c} of 5.6%, mean BMI of 37.3 kg/m^2, mean baseline weight of 102.9 kg, and mean eGFR of 95.8 mL/min/1.73 m^2. The minority of subjects (27.2%) lost more than 2 kg during the 4-week run-in period. Overall, baseline characteristics were generally similar across treatment groups.

Results:

Table 1 below, summarizes the effect of co-therapy of canagliflozin 300 mg / phentermine 15 mg versus placebo on body weight and systolic blood pressure (SBP).

Table 1: Results: Combination Treatment (canagliflozin 300 mg / phentermine 15 mg) vs Placebo (Week 26)

Endpoint	Difference[b]	(95% CI)[b]	p-value[a]
Body Weight, % change from baseline	-6.9	(-8.6;-5.2)	<0.001
Proportions of subjects with weight loss ≥ 5%	49.1	(32.2;66.1)	<0.001
Body Weight at Week 26 Absolute change from baseline	-6.7	(-8.5;-4.9)	<0.001
SBP at Week 26 Absolute change from baseline	-4.2	(-7.7;-0.8)	0.015

[a] Nominal p-value

[b] Difference in proportions for achieving weight loss ≥ 5% endpoint; difference of LS Means for all other endpoints

NOTE: For percent change from baseline in weight, absolute change from baseline in weight, and change from baseline in SBP, CIs and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, weight loss during run-in, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect. For achieving at least 5% weight loss, CI is based on Normal approximation to binomial distribution with continuity correction; p-value is based on the generalized linear mixed model for repeated measures including the fixed effects of treatment, weight loss during run-in, visit, treatment-by-visit interaction, treatment-by-subgroup interaction, baseline value and baseline-by-visit interaction, and subject as a random effect.

Treatment with co-therapy of canagliflozin 300 mg / phentermine 15 mg achieved statistical significance versus placebo with respect to the percent

change from baseline in weight at Week 26 (-7.5% vs 0.6%, respectively, $p < 0.001$). The primary weight loss endpoint at week 26, as measured, is shown in a graph of observed weight loss (as the mean placebo-subtracted weight loss at each time point) in Figure 1, open symbols. More specifically, co-administration of 300 mg canagliflozin and 15 mg phentermine was associated with a statistically significant placebo-subtracted weight loss of -6.9%. Additionally, at the endpoint of Week 26, no plateau in weight loss was observed, indicating that weight loss would be expected to continue beyond Week 26. The proportion of subjects who achieved at least 5% weight reduction was 66.7% in the co-administration arm, compared to 17.5% for placebo. The proportion of subjects with a weight loss of at least 10% was 34.9% in the co-administration group, vs. 8.8% with placebo. (Thus, at Week 26, the study met both benchmarks considered effective for weight management by the FDA: "after 1 year of treatment either of the following occurs: the difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant, or the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.) Based on the Week 26 weight loss over time data measured in in the study, extrapolation (exponential fit) to estimate weight loss at 1 year, indicated a potential placebo-subtracted weight loss of -8.8% for the co-administration group, as shown by the solid line in Figure 1.

It is estimated that with respect to the weight loss observed at Week 26, phentermine alone contributes 50%, canagliflozin alone contributes 18% and the interaction contributes 32%.

Table 2 below provides percent change from baseline for body weight at Week 26 for each of the treatment groups of the study: (A) combination treatment with canagliflozin 300 mg and phentermine 15 mg, (B) canagliflozin 300 mg, (C) phentermine 15 mg and (D) placebo.

Table 2: % Change from Baseline, Body Weight at Week 26

	Placebo (N=82)	Phen 15 mg (N=85)	Cana 300 mg (N=84)	Cana 300mg / Phen 15 mg (N=83)
Weight (kg) Value at Baseline				
N	76	76	78	77
Mean (SD)	104.00 (18.344)	102.43 (18.606)	103.33 (19.626)	100.06 (18.125)
% Change from Baseline at Week 26				
LS Mean (SE)	-0.6 (0.6)	-4.1 (0.6)	-1.9 (0.6)	-7.5 (0.6)
Minus Placebo[a]				
P-value		<0.001	0.142	<0.001
Diff. of LS Means (SE)		-3.5 (0.9)	-1.3 (0.9)	-6.9 (0.9)
95% CI[a]		(-5.3;-1.8)	(-3.1;0.4)	(-8.6;-5.2)
Minus Phentermine 15 mg[a]				
P-value				<0.001
Diff. of LS Means (SE)				-3.4 (0.9)
95% CI[a]				(-5.1;-1.6)
Minus Canagliflozin 300 mg[a]				
P-value				<0.001
Diff. of LS Means (SE)				-5.6 (0.9)
95% CI[a]				(-7.3;-3.8)

[a]Pairwise comparison: CIs and P values are based on a mixed model for repeated measures including the fixed effects of treatment, weight loss during run-in, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect.

Note: The table includes only the subjects who had both baseline and post-baseline body weight measurements.

The change from baseline in absolute body weight at Week 26 was analyzed with an MMRM similar to the primary efficacy endpoint. The categorical secondary efficacy endpoint (proportion of subjects with weight loss

≥5% at Week 26) was analyzed with a generalized linear mixed model which is similar to the MMRM approach, though suitable for longitudinal binary data, with results as shown in Table 3, below.

Table 3: Absolute Body Weight Change from Baseline, Week 26

	Placebo (N=82)	Phen 15 mg (N=85)	Cana 300 mg (N=84)	Cana 300 mg / Phen 15 mg (N=83)
Weight (kg) Value at Baseline				
N	76	76	78	77
Mean (SD)	104.00 (18.344)	102.43 (18.606)	103.33 (19.626)	100.06 (18.125)
Change from Baseline at Week 26				
LS Mean (SE)	-0.6 (0.6)	-4.1 (0.6)	-1.9 (0.7)	-7.3 (0.6)
Minus Placebo[a]				
P-value		<0.001	0.153	<0.001
Diff. of LS Means (SE)		-3.5 (0.9)	-1.3 (0.9)	-6.7 (0.9)
95% CI (a)		(-5.3;-1.7)	(-3.1;0.5)	(-8.5;-4.9)
Minus Phen 15 mg[a]				
P-value				<0.001
Diff. of LS Means (SE)				-3.2 (0.9)
95% CI (a)				(-4.9;-1.4)
Minus Cana 300 mg[a]				
P-value				<0.001
Diff. of LS Means (SE)				-5.4 (0.9)
95% CI (a)				(-7.1;-3.6)

[a]Pairwise comparison: CIs and P values are based on a mixed model for repeated measures including the fixed effects of treatment, weight loss during run-in, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect.

Note: The table includes only the subjects who had both baseline and post-baseline body weight measurements.

In addition to the effect on weight loss, a significant placebo-subtracted reduction in systolic blood pressure of -4.2 mm Hg (baseline 125 mm Hg) was observed in the co-administration treatment group (the absolute change in SBP at Week 26 was -6.9 mmHg vs. -2.7 mmHg for the placebo controlled group, p = 0.015). The reduction in diastolic blood pressure of -1.6 mm Hg (baseline 80 mm Hg) was not statistically significant. The change from baseline in systolic blood pressure at Week 26 was analyzed with an MMRM similar to the primary efficacy endpoint, with results as shown in Table 4, below.

Table 4: Change From Baseline, Systolic Blood Pressure, Week 26

	Placebo (N=82)	Phen 15 mg (N=85)	Cana 300 mg (N=84)	Cana 300 mg / Phen 15 mg (N=83)
Systolic blood pressure (mmHg), Value at Baseline				
N	75	76	78	77
Mean (SD)	124.22 (12.937)	124.05 (11.491)	124.81 (13.309)	125.26 (13.068)
Change From Baseline				
LS Mean (SE)	-2.7 (1.3)	-1.4 (1.2)	-3.1 (1.3)	-6.9 (1.2)
Minus Placebo[a]				
P-value		0.456	0.827	0.015
Diff. of LS Means (SE)		1.3 (1.8)	-0.4 (1.8)	-4.2 (1.7)
95% CI (a)		(-2.1;4.8)	(-3.9;3.1)	(-7.7;-0.8)
Minus Phen 15 mg[a]				
P-value				0.001
Diff. of LS Means (SE)				-5.6 (1.7)
95% CI (a)				(-8.9;-2.2)
Minus Cana 300 mg[a]				
P-value				0.028
Diff. of LS Means (SE)				-3.9 (1.7)
95% CI (a)				(-7.3;-0.4)

[a]Pairwise comparison: CIs and P values are based on a mixed model for repeated measures including the fixed effects of treatment, weight loss during run-in, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect.

Note: The table includes only the subjects who had both baseline and post-baseline systolic blood pressure measurements.

The treatment arms containing phentermine 15 mg also appeared to increase pulse at Week 26, consistent with the known effects of phentermine (LS Mean change from baseline (SE) = 4.1 (1.0) bpm and 3.5 (0.9) bpm for phentermine 15 mg and canagliflozin 300 mg/phentermine 15 mg, respectively, compared to -0.7 (1.0) bpm in the placebo group, and 0.7 (1.0) in the canagliflozin 300 mg group). Table 5 shows the mean and mean change from baseline for systolic blood pressure, diastolic blood pressure and pulse rate at Week 26.

Table 5: Mean & Mean Change for Blood Pressure, Pulse Rate at Week 26

	Placebo (N=82)	Phen 15 mg (N=85)	Cana 300 mg (N=84)	Cana 300 mg / Phen 15 mg (N=83)
Systolic Blood Pressure (mmHg)				
N	57	60	56	63
Mean baseline	125.27	123.39	124.70	125.28
Mean change (SD)	-3.09 (10.967)	-1.13 (10.007)	-3.31 (11.349)	-7.08 (10.128)
(95% CI)	(-6.003; -0.184)	(-3.718; 1.452)	(-6.349; -0.270)	(-9.635; -4.534)
Median change	-2.00	-0.33	-1.67	-6.00
(95% CI)	(-6.000; 0.333)	(-3.000; 2.000)	(-6.000; 0.000)	(-8.333; -3.667)
Diastolic Blood Pressure (mmHg)				
N	57	60	56	63
Mean baseline	80.15	78.54	79.26	79.35
Mean change (SD)	-1.08 (7.692)	0.55 (6.864)	-1.32 (6.779)	-2.32 (6.705)
(95% CI)	(-3.123; 0.959)	(-1.223; 2.323)	(-3.131; 0.500)	(-4.006; -0.629)
Median change	-0.33	0.67	-1.17	-0.67

(95% CI)	(-4.000; 1.667)	(-1.667; 2.667)	(-3.333; 0.333)	(-3.333; 0.333)
Pulse Rate (BEATS/MIN)				
N	57	60	56	63
Mean baseline	72.96	70.11	69.37	73.42
Mean change (SD)	-0.89 (7.059)	5.02 (7.568)	1.64 (6.786)	3.23 (9.800)
(95% CI)	(-2.762; 0.984)	(3.067; 6.977)	(-0.175; 3.460)	(0.760; 5.696)
Median change	-1.00	4.67	0.83	3.67
(95% CI)	(-4.000; 1.333)	(1.667; 6.667)	(-1.000; 2.667)	(0.667; 5.333)

Note: For each measurement, only the subjects who had both baseline and post baseline measurements are included.

Formulation Example 1 – Prophetic Example

As a specific embodiment of an oral composition, 300 mg of canagliflozin and 15 mg of phentermine are formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

Formulation Example 2 – Prophetic Example

As a specific embodiment of an oral composition, 300 mg of canagliflozin and 15 mg of phentermine are formulated with lactose and microcrystalline cellulose to provide a tablet of total weight in the amount of about 600 mg to about 620 mg.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

We claim:

1. A method for treating, delaying, slowing the progression of or preventing obesity or an obesity related disorder comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

2. A method for treating obesity, promoting weight loss, suppressing appetite, decreasing food intake, inducing satiety or controlling weight gain comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy consisting essentially of

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

3. A method for treating, delaying, slowing the progression of or preventing a metabolic disorder comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

4. A method for treating, delaying, slowing the progression of and / or preventing a renal or fatty liver disorder comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

5. A method for providing cardiovascular protection comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

6. A method for treating, delaying, slowing the progression of or preventing a major adverse cardiovascular event (MACE) comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

7. A method for decreasing blood pressure comprising administering to a subject in need thereof, co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

8. A method for treating or preventing sleep apnea comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

9. A method for prolonging the life or life span of a subject comprising administering to the subject co-therapy comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day; and

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day.

10. A method as in any of Claims 1-9 wherein the subject in need thereof is overweight or obese.

11. A method as in any of Claims 1-9 further comprising identifying the subject in need thereof by determining the subject's body mass index (BMI).

12. A method as in any of Claims 1-9 wherein the subject in need thereof is a subject whose body mass index is greater than or equal to about 25 kg/m^2.

13. A method as in any of Claims 1-9, wherein the subject achieves a weight loss after 26 Weeks of between about 5% and about 10%.

14. A method as in any of Claims 1-9, wherein the subject in need thereof is a subject who (a) has measured body mass index is greater than or equal to about 25 kg/m^2; (b) is a candidate for or has had bariatric surgery; or (c) is a candidate for or has had implanted a weight loss promoting device.

15. A method as in Claim 2, wherein the subject in need thereof is overweight or obese; and wherein the subject in need thereof has been diagnosed with or exhibits one or more symptoms of a disorder selected from the group consisting of pre-diabetes, impaired oral glucose tolerance, Type II diabetes mellitus, Metabolic Syndrome, cardiovascular risk, renal or fatty liver disorder and sleep apnea.

16. A method as in Claim 2, wherein the subject in need thereof has been diagnosed with or shows one or more symptoms of one or more of the following

conditions: (a) diabetes mellitus, regardless of type; (b) chronic kidney disease (CKD); (c) acute renal failure (ARF); (d) renal transplant recipients; (e) renal transplant donors; (f) unilateral total or partial nephrectomized patients; or (g) nephrotic syndrome.

17. A method as in Claim 2, wherein the subject in need thereof is

(1) an individual diagnosed with one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

(2) an individual who shows one, two or more of the following signs:

(a) a fasting blood glucose or serum glucose concentration greater than about 100 mg/dL, in particular greater than about 125 mg/dL;

(b) a postprandial plasma glucose equal to or greater than about 140 mg/dL;

(c) an HbA1c value equal to or greater than about 7.0%; or

(3) an individual wherein one, two, three or more of the following conditions are present:

(a) obesity, visceral obesity and/or abdominal obesity,

(b) triglyceride blood level equal to or greater than about 150 mg/dL,

(c) HDL-cholesterol blood level less than about 40 mg/dL in female patients and less than about 50 mg/dL in male patients,

(d) a systolic blood pressure equal to or greater than about 130 mm Hg and a diastolic blood pressure equal to or greater than about 85 mm Hg,

(e) a fasting blood glucose level equal to or greater than about 100 mg/dL.

18. A method as in Claim 2, wherein the subject in need thereof is diabetic or pre-diabetic.

19. A method as in Claim 2, wherein the subject in need thereof is non-diabetic.

20. A method as in any of Claims 1-9, wherein the subject in need thereof is a subject who is taking one or more pharmaceutical agents whose potential side effects include weight gain.

21. A method as in Claim 1, wherein the obesity related disorder is selected from the group consisting of a metabolic disorder, a renal or fatty liver disorder, a cardiovascular event, and sleep apnea.

22. A method as in Claim 3, wherein the metabolic disorder is selected from the group consisting of hyperglycemia, pre-diabetes, impaired oral glucose tolerance, impaired fasting blood glucose, post prandial hyperglycemia, hyperinsulinemia, insulin resistance, Type 2 diabetes mellitus, Type 1 diabetes, MODY, LADA, NODAT, gestational diabetes, insufficient glycemic control and Syndrome X.

23. A method as in Claim 3, wherein the metabolic disorder is selected from the group consisting of pre-diabetes, impaired oral glucose tolerance, impaired fasting blood glucose, insulin resistance, Type 2 diabetes mellitus and Syndrome X.

24. A method as in Claim 3, wherein the metabolic disorder is Type 2 diabetes mellitus.

25. A method as in Claim 4, wherein the renal or fatty liver disorder is selected from the group consisting of alcoholic simple fatty liver, alcoholic steatohepatitis (ASH), alcoholic hepatic fibrosis, alcoholic cirrhosis, nonalcoholic fatty liver disease (NAFLD), nonalcoholic simple fatty liver, nonalcoholic steatohapatitis (NASH), nonalcoholic hepatic fibrosis, and nonalcoholic cirrhosis.

26. A method as in Claim 4, wherein the renal or fatty liver disorder is selected from the group consisting of hyperfiltrative diabetic nephropathy, renal hyperfiltration, glomerular hyperfiltration, renal allograft hyperfiltration, compensatory hyperfiltration, hyperfiltrative chronic kidney disease and hyperfiltrative acute renal failure.

27. A method as in Claim 4, wherein the renal or fatty liver disorder is selected from the group consisting of microalbuminuria, macroalbuminuria, elevated urine albumin levels and elevated albumin/creatinine ratio (ACR).

28. A method as in Claim 4, wherein the renal or fatty liver disorder is selected from the group consisting of NASH and NAFLD.

29. A method as in Claim 4, wherein the renal disorder is diabetic nephropathy.

30. A method as in Claim 6, wherein the major adverse cardiovascular event (MACE) is selected from the group consisting of myocardial infarction, unstable angina, cardiovascular death, revascularization, fatal or non-fatal cerebrovascular accident, peripheral arteriopathy, aortic event and hospitalization due to congestive heart failure.

31. A method as in Claim 6, wherein the major adverse cardiovascular event (MACE) is selected from the group consisting of myocardial infarction, fatal or non-fatal cerebrovascular accident and hospitalization due to congestive heart failure.

32. A method as in Claim 6, wherein the major adverse cardiovascular event (MACE) is myocardial infarction or fatal or non-fatal cerebrovascular accident.

33. A method as in Claim 7, wherein the blood pressure elevated systolic blood pressure.

34. A method as in any of Claims 1-9, wherein the canagliflozin is administered as a crystalline hemihydrate.

35. A method as in any of Claims 1-9, wherein the canagliflozin is administered in an amount in the range of from about 100 to about 300 mg.

36. A method as in any of Claims 1-9, wherein the canagliflozin is administered in an amount of about 100 mg or about 300 mg.

37. A method as in any of Claim 1-9, wherein the phentermine is phentermine hydrochloride.

38. A method as in any of Claims 1-9, wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 37.5 mg.

39. A method as in any of Claims 1-9, wherein the phentermine is administered in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg or about 37.5 mg.

40. A method as in any of Claims 1-9, wherein the phentermine is administered in an amount of about 3.75 mg, about 7.5 mg or about 15 mg.

41. A method as in any of Claims 1-9, wherein the canagliflozin is administered as a crystalline hemihydrate; wherein the canagliflozin is administered in an amount in the range of from about 100 to about 300 mg; wherein the phentermine is administered as phentermine hydochloride; and wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 37.5 mg.

42. A method as in any of Claims 1-9, wherein the canagliflozin is administered as a crystalline hemihydrate; wherein the canagliflozin is administered in an amount of about 100 mg or about 300 mg; wherein the

phentermine is administered as phentermine hydrochloride; and wherein the phentermine is administered in an amount of about 3.75 mg, about 7.5 mg, about 15 mg, about 30 mg or about 37.5 mg.

43. A method as in any of Claims 1-9, wherein the canagliflozin is administered as a crystalline hemihydrate; wherein the canagliflozin is administered in an amount of about 100 mg or about 300 mg; wherein the phentermine is administered as phentermine hydrochloride; and wherein the phentermine is administered in an amount of about 3.75 mg, about 7.5 mg or about 15 mg.

44. A method as in any of Claims 1-9, wherein the canagliflozin is administered as a crystalline hemihydrate; wherein the canagliflozin is administered in an amount of about 300 mg; wherein the phentermine is administered as phentermine hydrochloride; and wherein the phentermine is administered in an amount of about 15 mg.

45. A pharmaceutical composition comprising

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day;

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day; and

(c) a pharmaceutically acceptable carrier or excipient.

46. A pharmaceutical composition made by mixing

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day;

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day; and

(c) a pharmaceutically acceptable carrier or excipient.

47. A process for making a pharmaceutical composition comprising mixing

(a) canagliflozin; wherein the canagliflozin is administered in an amount in the range of from about 50 mg to about 500 mg per day;

(b) phentermine; wherein the phentermine is administered in an amount in the range of from about 3.75 mg to about 50 mg per day; and

(c) a pharmaceutically acceptable carrier or excipient.

48. A method for treating, delaying, slowing the progression or preventing obesity or an obesity related disorders as described herein.

49. A method or pharmaceutical composition as described herein.

50. A method for chronic weight management comprising administering to a subject in need thereof a therapeutically effective amount of co-therapy comprising (a) canagliflozin and (b) phentermine;

wherein the subject in need thereof is a subject with an initial body mass index greater than or equal to about 30 kg/m^2; or greater than or equal to about 27 kg/m^2 and diagnosed with or exhibiting at least one weight-related co-morbid condition.

51. The method of claim 50, wherein the co-therapy is an adjunct to a reduced-calorie diet and increased physical activity.

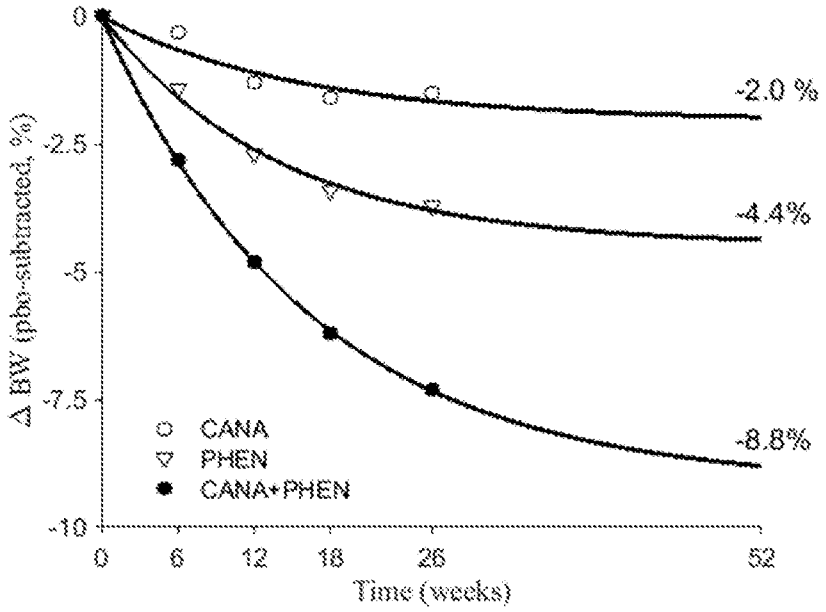


Figure 1: Mean placebo-subtracted weight loss (measured at 0-26 Weeks, extrapolated to 52 Weeks) for Canagliflozin, Phentermine and Combiantion Therapy

5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/051435

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/137 A61K31/7042 A61P3/04 A61P3/00 A61P9/00
A61P9/12 A61P13/00 A61P1/16 A61P43/00
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, BIOSIS, WPI Data, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LOTFI KATAYOUN ET AL: "Case Study: Weight loss in a patient with type 2 diabetes: Challenges of diabetes management.", OBESITY (SILVER SPRING, MD.) APR 2015, vol. 23 Suppl 1, April 2015 (2015-04), pages S11-S12, XP002764434, ISSN: 1930-739X the whole document ----- -/--	1-18, 20-33, 48-51

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2016	05/12/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Houyvet-Landriscina

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROSENTHAL NORM ET AL: "Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus.", ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 1358, 25 August 2015 (2015-08-25), pages 28-43, XP002764435, ISSN: 1749-6632 abstract page 41, column 1, paragraph 2 -----	1-51
X	"Effects of Co-administration of Canagliflozin 300 mg and Phentermine 15 mg With Placebo in the Treatment of Non-Diabetic Overweight and Obese Participants", clinicaltrials.gov , 10 August 2015 (2015-08-10), XP002764436, Retrieved from the Internet: URL:https://clinicaltrials.gov/archive/NCT02243202/2015_08_10 [retrieved on 2016-11-16] the whole document -----	1-51
Y	WO 2011/142478 A1 (MITSUBISHI TANABE PHARMA CORP [JP]; SUGIMOTO MASAAKI; KINOSHITA HAJIME) 17 November 2011 (2011-11-17) page 1, lines 5-23 page 2, line 19 - page 3, line 10 page 10, line 35 - page 11, line 3 claim 14 -----	1-51
Y	GABRIEL UWAIFO ET AL: "Phentermine and topiramate for the management of obesity: a review", DRUG DESIGN, DEVELOPMENT AND THERAPY, 1 April 2013 (2013-04-01), page 267, XP055320698, DOI: 10.2147/DDDT.S31443 abstract page 269, column 1, paragraph 3 - page 270, column 2, paragraph 1 ----- -/--	1-51

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JAMES R. TAYLOR ET AL: "New and Emerging Pharmacologic Therapies for Type 2 Diabetes, Dyslipidemia, and Obesity", CLINICAL THERAPEUTICS., vol. 35, no. 1, 1 January 2013 (2013-01-01), pages A3-A17, XP055320084, US ISSN: 0149-2918, DOI: 10.1016/j.clinthera.2012.12.012 abstract table I pages A6-A7 tables IV-V -----	1-51
X,P	ClinicalTrials.gov: "Effects of Co-administration of Canagliflozin 300 mg and Phentermine 15 mg With Placebo in the Treatment of Non-Diabetic Overweight and Obese Participants", www.clinicaltrials.gov , 16 June 2016 (2016-06-16), XP002764437, Retrieved from the Internet: URL:https://www.clinicaltrials.gov/ct2/show/results/NCT02243202?term=NCT02243202&rank=1 [retrieved on 2016-11-16] the whole document -----	1-51
X,P	Alex Morrisson: "Canagliflozin, Phentermine Combo Provides Greater Weight Loss vs Placebo for Obese Adults", DGnews , 16 June 2016 (2016-06-16), XP002764438, Retrieved from the Internet: URL:http://dgnews.docguide.com/canagliflozin-phentermine-combo-provides-greater-weight-loss-vs-placebo-obese-adults [retrieved on 2016-11-16] the whole document -----	1-51

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/051435

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011142478 A1	17-11-2011	CN 102985075 A	20-03-2013
		CN 105769792 A	20-07-2016
		EP 2568971 A1	20-03-2013
		JP 5596799 B2	24-09-2014
		JP 2013526482 A	24-06-2013
		KR 20130106279 A	27-09-2013
		TW 201200164 A	01-01-2012
		US 2013052266 A1	28-02-2013
		US 2016228375 A1	11-08-2016
		WO 2011142478 A1	17-11-2011

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 108024977 A
(43)申请公布日 2018.05.11

(21)申请号 201680053661.8

(22)申请日 2016.09.13

(30)优先权数据
62/218842 2015.09.15 US
62/306110 2016.03.10 US
15/262038 2016.09.12 US

(85)PCT国际申请进入国家阶段日
2018.03.15

(86)PCT国际申请的申请数据
PCT/US2016/051435 2016.09.13

(87)PCT国际申请的公布数据
WO2017/048670 EN 2017.03.23

(71)申请人 詹森药业有限公司
地址 比利时比尔斯特恩豪特斯路30号

(72)发明人 N.R.罗森塔 P.罗斯恩伯格 D.C.波里多里 D.K.韦斯 P.P.斯泰恩

(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 刘力 黄希贵

(51)Int.Cl.
A61K 31/137(2006.01)
A61K 31/7042(2006.01)
A61P 3/04(2006.01)
A61P 3/00(2006.01)
A61P 9/00(2006.01)
A61P 9/12(2006.01)
A61P 13/00(2006.01)
A61P 1/16(2006.01)
A61P 43/00(2006.01)

权利要求书4页 说明书38页 附图1页

(54)发明名称

用于治疗肥胖症和肥胖症相关疾病的包含卡格列净和芬特明的协同治疗

(57)摘要

本发明涉及包含卡格列净和芬特明的协同治疗用于治疗肥胖症和肥胖症相关疾病的用途。更具体地，本发明涉及协同治疗，其用于治疗肥胖症、促进体重减轻和/或抑制食欲；用于治疗、延迟、减慢代谢紊乱的进程和/或预防代谢紊乱(包括例如2型糖尿病)；用于治疗、延迟、减慢肾或脂肪肝疾病的进程和/或预防肾或脂肪肝疾病(包括例如NASH、NAFLD等)；用于治疗、延迟、减慢睡眠障碍的进程和/或预防睡眠障碍(包括例如睡眠呼吸暂停)；用于提供心血管保护；用于治疗、延迟、减慢心血管事件的进程和/或预防心血管事件(包括主要不良心脏事件(MACE)诸如心肌梗塞、不稳定型心绞痛、心血管死亡、脉管再通、致命或非致命脑血管意外、外周动脉病、主动脉事件和由于充血性心力衰竭的住院等)；和/或扩展或延长寿命。

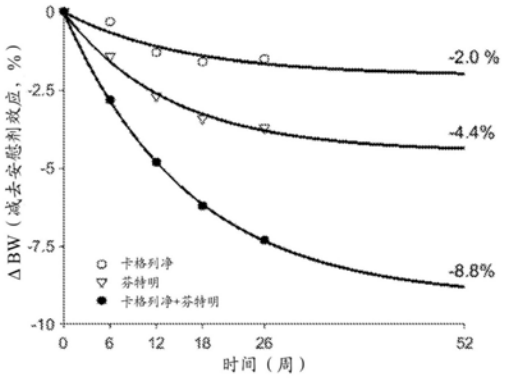


图1：卡格列净、芬特明和联合治疗的减去安慰剂效应的平均体重减轻（在0-26周，外推至52周时测量）

CN 108024977 A

1.一种用于治疗、延迟、减慢肥胖症或肥胖症相关疾病的进程或预防肥胖症或肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

2.一种用于治疗肥胖症、促进体重减轻、抑制食欲、减少食物摄取、引起饱腹感或控制体重增加的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗基本由以下组成:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

3.一种用于治疗、延迟、减慢代谢紊乱的进程或预防代谢紊乱的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

4.一种用于治疗、延迟、减慢肾或脂肪肝疾病的进程和/或预防肾或脂肪肝疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

5.一种用于提供心血管保护的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

6.一种用于治疗、延迟、减慢主要不良心血管事件(MACE)的进程或预防主要不良心血管事件的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

7.一种用于降低血压的方法,所述方法包括向对其有需要的受检者施用协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

8.一种用于治疗或预防睡眠呼吸暂停的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

9.一种用于延长受检者的生命或寿命的方法,所述方法包括向受检者施用协同治疗,所述协同治疗包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;以及

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用。

10.根据权利要求1至9中任一项所述的方法，其中所述对其有需要的受检者超重或肥胖。

11.根据权利要求1至9中任一项所述的方法，所述方法还包括通过测定所述受检者的身体质量指数(BMI)来识别所述对其有需要的受检者。

12.根据权利要求1至9中任一项所述的方法，其中所述对其有需要的受检者为其身体质量指数大于或等于约25kg/m^2的受检者。

13.根据权利要求1至9中任一项所述的方法，其中所述受检者在26周之后达到介于约5％和约10％之间的体重减轻。

14.根据权利要求1至9中任一项所述的方法，其中所述对其有需要的受检者为如下受检者：(a)具有大于或等于约25kg/m^2的经测量的身体质量指数；(b)为减肥手术的候选者或已经经过减肥手术；或者(c)为体重减轻促进装置的候选者或已经植入体重减轻促进装置。

15.根据权利要求2所述的方法，其中所述对其有需要的受检者超重或肥胖；并且其中所述对其有需要的受检者经诊断患有或表现出选自下列的疾病的一种或多种症状：糖尿病前期、口服葡萄糖耐量受损、II型糖尿病、代谢综合征、心血管风险、肾或脂肪肝疾病以及睡眠呼吸暂停。

16.根据权利要求2所述的方法，其中所述对其有需要的受检者经诊断患有或表现出以下一种或多种病症的一种或多种症状：(a)糖尿病，无论何种类型；(b)慢性肾病(CKD)；(c)急性肾衰竭(ARF)；(d)肾移植受者；(e)肾移植供者；(f)单侧肾全部或部分切除的患者；或者(g)肾病综合征。

17.根据权利要求2所述的方法，其中所述对其有需要的受检者是：

(1)诊断出患有选自下列的病症中的一种或多种的个体：超重、肥胖症、内脏型肥胖症和腹部肥胖症；或者

(2)表现出以下病征中的一种、两种或更多种的个体：

(a)空腹血液葡萄糖或血清葡萄糖浓度大于约100mg/dL，尤其是大于约125mg/dL；

(b)餐后血浆葡萄糖等于或大于约140mg/dL；

(c)HbA1c值等于或大于约7.0％；或者

(3)存在以下病症中的一种、两种、三种或更多种的个体：

(a)肥胖症、内脏型肥胖症和/或腹部肥胖症，

(b)血液甘油三酯水平等于或大于约150mg/dL，

(c)女性患者的血液HDL-胆固醇水平小于约40mg/dL，以及男性患者的血液HDL-胆固醇水平小于约50mg/dL，

(d)收缩压等于或大于约130mmHg，以及舒张压等于或大于约85mmHg，

(e)空腹血液葡萄糖水平等于或大于约100mg/dL。

18.根据权利要求2所述的方法，其中所述对其有需要的受检者是糖尿病的或糖尿病前期的。

19.根据权利要求2所述的方法，其中所述对其有需要的受检者是非糖尿病的。

20.根据权利要求1至9中任一项所述的方法，其中所述对其有需要的受检者是服用一种或多种其潜在副作用包括体重增加的药剂的受检者。

21.根据权利要求1所述的方法，其中所述肥胖症相关的疾病选自：代谢紊乱、肾或脂肪

肝疾病、心血管事件、和睡眠呼吸暂停。

22.根据权利要求3所述的方法，其中所述代谢紊乱选自：高血糖、糖尿病前期、口服葡萄糖耐量受损、空腹血液葡萄糖受损、餐后高血糖、高胰岛素血症、胰岛素抵抗、2型糖尿病、1型糖尿病、MODY、LADA、NODAT、妊娠期糖尿病、血糖控制不足和X综合征。

23.根据权利要求3所述的方法，其中所述代谢紊乱选自：糖尿病前期、口服葡萄糖耐量受损、空腹血液葡萄糖受损、胰岛素抵抗、2型糖尿病和X综合征。

24.根据权利要求3所述的方法，其中所述代谢紊乱为2型糖尿病。

25.根据权利要求4所述的方法，其中所述肾或脂肪肝疾病选自：酒精性单纯性脂肪肝、酒精性脂肪性肝炎(ASH)、酒精性肝纤维化、酒精性肝硬化、非酒精性脂肪肝病(NAFLD)、非酒精性单纯性脂肪肝、非酒精性脂肪性肝炎(NASH)、非酒精性肝纤维化和非酒精性肝硬化。

26.根据权利要求4所述的方法，其中所述肾或脂肪肝疾病选自：过度滤过性糖尿病性肾病、肾过度滤过、肾小球过度滤过、肾同种异体移植过度滤过、代偿性过度滤过、过度滤过性慢性肾病和过度滤过性急性肾衰竭。

27.根据权利要求4所述的方法，其中所述肾或脂肪肝疾病选自：微量白蛋白尿、大量白蛋白尿、高尿白蛋白水平和高白蛋白/肌酸酐比率(ACR)。

28.根据权利要求4所述的方法，其中所述肾或脂肪肝疾病选自：NASH和NAFLD。

29.根据权利要求4所述的方法，其中所述肾疾病为糖尿病性肾病。

30.根据权利要求6所述的方法，其中所述主要不良心血管事件(MACE)选自：心肌梗塞、不稳定型心绞痛、心血管死亡、脉管再通、致命或非致命脑血管意外、外周动脉病、主动脉事件和由于充血性心力衰竭的住院。

31.根据权利要求6所述的方法，其中所述主要不良心血管事件(MACE)选自：心肌梗塞、致命或非致命脑血管意外和由于充血性心力衰竭的住院。

32.根据权利要求6所述的方法，其中所述主要不良心血管事件(MACE)为心肌梗塞或致命或非致命脑血管意外。

33.根据权利要求7所述的方法，其中所述血压为升高的收缩压。

34.根据权利要求1至9中任一项所述的方法，其中所述卡格列净以结晶半水合物形式施用。

35.根据权利要求1至9中任一项所述的方法，其中所述卡格列净以约100mg至约300mg范围内的量施用。

36.根据权利要求1至9中任一项所述的方法，其中所述卡格列净以约100mg或约300mg的量施用。

37.根据权利要求1至9中任一项所述的方法，其中所述芬特明为芬特明盐酸盐。

38.根据权利要求1至9中任一项所述的方法，其中所述芬特明以约3.75mg至约37.5mg范围内的量施用。

39.根据权利要求1至9中任一项所述的方法，其中所述芬特明以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量施用。

40.根据权利要求1至9中任一项所述的方法，其中所述芬特明以约3.75mg、约7.5mg或约15mg的量施用。

41.根据权利要求1至9中任一项所述的方法，其中所述卡格列净以结晶半水合物形式

施用;其中所述卡格列净以约100mg至约300mg范围内的量施用;其中所述芬特明以芬特明盐酸盐形式施用;并且其中所述芬特明以约3.75mg至约37.5mg范围内的量施用。

42.根据权利要求1至9中任一项所述的方法,其中所述卡格列净以结晶半水合物形式施用;其中所述卡格列净以约100mg或约300mg的量施用;其中所述芬特明以芬特明盐酸盐形式施用;并且其中所述芬特明以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量施用。

43.根据权利要求1至9中任一项所述的方法,其中所述卡格列净以结晶半水合物形式施用;其中所述卡格列净以约100mg或约300mg的量施用;其中所述芬特明以芬特明盐酸盐形式施用;并且其中所述芬特明以约3.75mg、约7.5mg或约15mg的量施用。

44.根据权利要求1至9中任一项所述的方法,其中所述卡格列净以结晶半水合物形式施用;其中所述卡格列净以约300mg的量施用;其中所述芬特明以芬特明盐酸盐形式施用;并且其中所述芬特明以约15mg的量施用。

45.一种药物组合物,所述药物组合物包含:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用;以及

(c)药学上可接受的载体或赋形剂。

46.一种通过将以下物质混合制备的药物组合物:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用;以及

(c)药学上可接受的载体或赋形剂。

47.一种用于制备药物组合物的方法,所述方法包括将以下物质混合:

(a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量施用;

(b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量施用;以及

(c)药学上可接受的载体或赋形剂。

48.一种如本文所述的用于治疗、延迟、减慢肥胖症或肥胖症相关疾病的进程或预防肥胖症或肥胖症相关疾病的方法。

49.一种如本文所述的方法或药物组合物。

50.一种用于长期体重管理的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含(a)卡格列净和(b)芬特明;

其中所述对其有需要的受检者为以下受检者:初始身体质量指数大于或等于约30kg/m^2;或大于或等于约27kg/m^2,并且诊断患有或表现出至少一种体重相关的共病病症。

51.根据权利要求50所述的方法,其中所述协同治疗为低卡路里饮食和增加身体活动的助剂。

用于治疗肥胖症和肥胖症相关疾病的包含卡格列净和芬特明的协同治疗

[0001] 相关申请的交叉引用

[0002] 本专利申请要求2015年9月15日提交的美国临时专利申请62/218,842和2016年3月10日提交的美国临时专利申请62/306,110的优先权,其公开内容全文以引用方式并入本文中。

技术领域

[0003] 本发明涉及包含卡格列净和芬特明的协同治疗用于治疗肥胖症和肥胖症相关疾病的用途。更具体地,本发明涉及协同治疗,其用于治疗肥胖症、促进体重减轻和/或抑制食欲;用于治疗、延迟、减慢代谢紊乱的进程和/或预防代谢紊乱(包括例如2型糖尿病);用于治疗、延迟、减慢肾或脂肪肝疾病的进程和/或预防肾或脂肪肝疾病(包括例如NASH、NAFLD等);用于治疗、延迟、减慢睡眠障碍的进程和/或预防睡眠障碍(包括例如睡眠呼吸暂停);用于提供心血管保护;用于治疗、延迟、减慢心血管事件的进程和/或预防心血管事件(包括主要不良心脏事件(MACE)诸如心肌梗塞、不稳定型心绞痛、心血管死亡、脉管再通、致命或非致命脑血管意外、外周动脉病、主动脉事件和由于充血性心力衰竭的住院等);和/或扩展或延长寿命。

背景技术

[0004] 肥胖症是一种脂肪组织质量过量的状态。尽管通常被视为等同于增加体重,但这不一定是这种情况-瘦且肌肉非常发达的个体根据任意标准可能是超重的,但不具有增加的肥胖症。体重在人群中连续分布,使得瘦和胖之间的医学上有意义的分布在一定程度上是任意的。因此,肥胖症更有效地通过评估其与发病率或死亡率的联系来定义。

[0005] 尽管不是肥胖症的直接量度,但用于判断肥胖症的最广泛使用的方法是身体质量指数(BMI),其等于重量/高度^2(以kg/m^{2}为单位)。用于量化肥胖症的其它方法包括人体测量(皮褶厚度)、比重测量(水下称重)、计算机断层扫描(CT)或磁共振成像(MRI)、和电阻抗。使用来自都市生活表(Metropolitan Life Table)的数据,男性和女性两者之间的所有身高和体格的中点的BMI在19kg/m^{2}至26kg/m^{2}的范围内;在相似的BMI下,女性具有比男性更多的体脂。基于实质发病率的明确数据,30的BMI最常被用作男性和女性两者的肥胖症的阈值。大规模流行病学研究表明,当BMI为≥25时,全因性、代谢和心血管发病率开始升高(尽管以较慢的速率),这表明应当降低的肥胖症的截止值。一些当局使用术语超重(而不是肥胖)描述BMI介于25或27和30之间的个体。介于25和30之间的BMI应当被视为是医学上显著的,并且值得治疗干预,尤其是在受肥胖症影响的风险因子(诸如高血压和葡萄糖耐受不良)的存在下。

[0006] 来自全国健康和营养调查(NHANES)的最近数据示出患有肥胖症(BMI＞30)的美国成年人群的百分比已经从14.5%(在1976年和1980年之间)增加至22.5%(在1998年和1994年之间)。在1998年和1991年之间,多达50%的≥20岁的美国成年人超重(定义为BMI＞25)。

因为显著的健康风险存在于BMI介于25和30之间的许多个体中，所以日益增加的医学上显著的肥胖症的患病引起了极大关注。肥胖症在女性和穷人中更加常见；儿童的患病率也以令人担忧的速率增加。

[0007] 肥胖症主要对健康具有不利影响。病态肥胖个体(＞200％理想体重)的死亡率增加多达十二倍。死亡率随肥胖症增加而升高，特别是当肥胖症与腹内脂肪增加相关时。还显而易见的是肥胖症影响特定器官系统的程度受易感性基因的影响，所述易感性基因在人群中不同。与具有正常体重的个体相比，肥胖个体由于各种原因过早死亡的风险增加50％-100％。在美国，每年超过300,000例死亡可能是由于肥胖症。

[0008] 患有肥胖症的患者还具有发展胰岛素抵抗或葡萄糖耐受不良(其可持续发展成2型糖尿病)的更高机会。还存在高血压、性功能障碍、头痛、抑郁和睡眠呼吸暂停的更高可能性。

[0009] 糖尿病是对于存在血液葡萄糖升高的医学术语。患有糖尿病的人要么不能产生胰岛素，产生太少的胰岛素，要么不能响应胰岛素，从而导致葡萄糖在血液中积累。糖尿病的最常见形式是2型糖尿病，曾被称为成年型糖尿病或非胰岛素依赖型糖尿病(NIDDM)，这在成年人的糖尿病中可占据＞90％。然而，随着年轻人群变得日益超重或肥胖，2型糖尿病在青少年和儿童中正变得越来越普遍。糖尿病也可涉及妊娠期糖尿病、1型糖尿病或自体免疫糖尿病，曾被称为青少年型糖尿病和11/2型糖尿病，也被称为成年人隐匿性自体免疫糖尿病或LADA。糖尿病的发生可能由于不良饮食习惯或缺乏身体活动(例如久坐的生活方式)、基因突变、胰腺损伤、药物(例如AIDS治疗)或化学品(例如甾体化合物)暴露或者疾病(例如囊胞性纤维症、唐氏综合征、库欣氏综合征)。导致糖尿病的两类稀有的基因缺陷被称为青少年的成年发病型糖尿病(MODY)和非典型糖尿病(ADM)。

[0010] II型糖尿病(非胰岛素依赖型糖尿病或NIDDM)是一种涉及葡萄糖代谢异常和胰岛素抵抗以及长期并发症的代谢紊乱，所述长期并发症涉及眼睛、肾脏、神经和血管。II型糖尿病通常在成年(中年或之后)发病，并被描述为身体不能产生足够的胰岛素(非正常胰岛素分泌)或者其不能有效利用胰岛素(在靶器官或组织中对胰岛素作用具有抗性)。更具体地讲，患有II型糖尿病的患者具有相对胰岛素缺乏。也就是说，在这些患者中，血浆胰岛素水平就绝对值而言为正常到高，然而就存在的血浆葡萄糖水平而言比预计的要更低。

[0011] II型糖尿病的特征在于以下临床病征或症状：血浆葡萄糖浓度持续升高或高血糖；多尿症；多渴症和/或多食症；慢性微血管并发症诸如视网膜病、肾病和神经病变；和大血管并发症，诸如高脂血和高血压，这可导致失明、终末期肾病、截肢和心肌梗塞。

[0012] X综合征，也被称为胰岛素抵抗综合征(IRS)、代谢综合征、或X代谢综合征，是一种显示II型糖尿病和心血管疾病发展的风险因子的疾病，包括葡萄糖耐受不良、高胰岛素血症和胰岛素抵抗、高甘油三酯血症、高血压和肥胖症。

[0013] II型糖尿病的诊断包括症状的评估和对尿液和血液中的葡萄糖的测量。血液葡萄糖水平测定对于确诊而言是必要的。更具体地讲，空腹血液葡萄糖水平测定是所使用的标准方法。然而，口服葡萄糖耐量试验(OGTT)被认为比空腹血液葡萄糖水平更灵敏。II型糖尿病与口服葡萄糖耐量受损(OGT)相关。OGTT因此可有助于诊断II型糖尿病，但通常对于糖尿病的诊断不是必要的(Emancipator K,Am J Clin Pathol 1999年11月;112(5):665-74;Type 2Diabetes Mellitus,Decision Resources Inc.,2000年3月)。OGTT允许对胰β-细胞

分泌功能和胰岛素敏感性作出估计，这有助于II型糖尿病的诊断并对该疾病的严重性或进程作出评估(例如，Caumo A，Bergman RN，Cobelli C，.J Clin Endocrinol Metab 2000，85(11)：4396-402)。更具体地讲，OGTT尤其有助于在具有多个边界空腹血液葡萄糖水平但尚未被诊断为糖尿病的患者确立高血糖的程度。此外，OGTT可用于检测具有II型糖尿病症状的患者，其中非正常碳水化合物代谢的可能性诊断已被明确确立或否定。

[0014] 因此，葡萄糖耐量受损可在个体中进行诊断，所述个体的空腹血液葡萄糖水平比II型糖尿病诊断所要求的更低，但在OGTT期间具有介于正常和糖尿病之间的血浆葡萄糖响应。葡萄糖耐量受损被认为是糖尿病前期病症，并且葡萄糖耐量受损(如由OGTT定义的)是II型糖尿病发展的强效预测因子(HAFFNER，S.M.，Diabet Med，1997年8月；14Suppl 3：S12-8)。

[0015] II型糖尿病是进行性疾病，其与胰功能减弱和/或其他与胰岛素相关的过程相关联，并随着血浆葡萄糖水平升高而恶化。因此，II型糖尿病通常具有长期的糖尿病前期阶段，并且多种病理生理机制可导致病态的高血糖和葡萄糖耐量受损，例如糖尿病前期阶段的葡萄糖利用和有效性、胰岛素作用和/或胰岛素产生异常(Goldberg RB，Med Clin North Am，1998年7月；82(4)：805-21)。

[0016] 与葡萄糖耐受不良相关的糖尿病前期状态还可与腹部肥胖症、胰岛素抵抗、高血脂和高血压的易感性相关，即，X综合征(Groop L，Forsblom C，Lehtovirta M，Am J Hypertens，1997年9月；10(9Pt 2)：172S-180S；Haffner SM，J Diabetes Complications 1997年3月-4月；11(2)：69-76；Beck-Nielsen H，Henriksen JE，Alford F，Hother-Nielson O，Diabet Med，1996年9月；13(9Suppl6)：S78-84)。

[0017] 因此，碳水化合物代谢缺陷对II型糖尿病和葡萄糖耐量受损的发病很关键(Dinneen SF，Diabet Med，1997年8月；14Suppl 3：S19-24)。事实上，存在从葡萄糖耐量受损和空腹葡萄糖耐量受损到决定性II型糖尿病的连续带(Ramlo-Halsted BA，Edelman SV，Prim Care，1999年12月；26(4)：771-89)。

[0018] 人们对有风险发展II型糖尿病的个体的早期干预关注于降低病态高血糖或葡萄糖耐量受损，这种早期干预可防止或延缓向II型糖尿病和相关并发症和/或X综合征的进程。因此，通过有效治疗口服葡萄糖耐量受损和/或高血液葡萄糖水平，人们可以防止或抑制该疾病向II型糖尿病或X综合征的进程。

[0019] 肾是位于背部中央附近的豆形器官。每个肾内约有一百万个称为肾单位的微小结构，它们能过滤血液。这些肾单位清除废物和多余的水，使之变成尿液。肾单位的损伤是肾病的重要形式。该损伤可使肾无法清除废物。一些损伤，例如与过度滤过相关的损伤最初通常没有明显症状，但可在数年内缓慢发生。

[0020] “过度滤过性假说”意味着对有限肾储备的过度需求引起了肾的适应性变化及最终病理变化，最后导致“肾单位衰竭”。在单个肾单位水平上，据推测过度滤过是从肾小球内高血压引起白蛋白尿并随后引起降低的肾小球滤过率(GFR)的事件链中的早期环节。在此基础上，过度滤过因此代表了后续肾损伤的风险，并可归类为肾病理现象的早期表现，通常称为过度滤过阶段。这种肾过度滤过可引起早期肾小球病变和微量白蛋白尿，微量白蛋白尿本身又可引起大量白蛋白尿和终末期肾病。

[0021] 过度滤过对肾功能衰退的影响已在肾移植受者和供者中及因获得性肾病而切除

单肾的患者中、而且在患有糖尿病的患者中受到最透彻地评估(Magee等人,Diabetologia 2009;52:691-697)。理论上,功能性肾单位数量的任何降低将引起适应性肾小球过度滤过,不论是遗传学上诱发、由外科手术诱发,还是由获得性肾病诱发。此外,已表明,即使肾实质是完整的(例如,在糖尿病的情况下),过度滤过也会在某些病理生理状况下发生。因此,医疗上需要以良好疗效对肾过度滤过性损伤进行干预。

[0022] 肌酸酐是磷酸肌酸在肌肉组织中的分解产物,并且通常在机体中以恒定速率产生。血清肌酸酐是肾健康状况的重要指标,因为它是肌肉代谢的易测副产物,并通过肾稳定不变地分泌。从血液中清除肌酸酐的过程首要由肾负责,肾主要采取肾小球过滤,以及近端肾小管分泌的方式进行该过程。一般很少发生或不会发生肾小管对肌酸酐的重吸收。如果肾中过滤不足,则血液肌酸酐水平会升高。因此,血液和尿液中的肌酸酐水平可用于计算肌酸酐清除率(CrCl),该值与肾小球滤过率(GFR)相关联。还可单独使用血液肌酸酐水平来估算GFR(eGFR)。GFR因为是肾功能的量度,而在临床上很重要。当连同尿素一起解读肌酸酐的血液(血浆)浓度时,可进行肾功能的替代估算。BUN与肌酸酐的比率(血液尿素与肌酸酐的比率)可指示除肾固有的那些问题之外的其它问题;例如,与肌酸酐不成比例地升高的尿素水平可指示肾前问题,诸如容量空竭。

[0023] 仅在功能性肾单位发生显著损伤时,才会观察到血液肌酸酐水平的升高。通过计算估算肾小球滤过率(eGFR)得出肾功能的估值。可使用血清肌酸酐浓度准确地计算eGFR。人血清肌酸酐的典型参考值范围是:女性0.5mg/dl至1.0mg/dl(约45μmol/l-90μmol/l),男性0.7mg/dl至1.2mg/dl(60μmol/l-110μmol/l)。血清肌酸酐水平随时间推移的趋势一般比绝对肌酸酐水平更重要。

[0024] 当服用ACE抑制剂(ACEi)或血管紧张素II受体拮抗剂(或血管紧张素受体阻断剂,ARB)时,肌酸酐水平可适度升高。同时使用ACE抑制剂和ARB会使肌酸酐水平升高到比单独使用这两种药物时更高的程度。使用ACE抑制剂或ARB时该水平预计会升高<30%。

[0025] 白蛋白尿是尿液中存在白蛋白的病症。健康个体的肾能过滤白蛋白。当肾无法正常地从尿液中过滤大分子(诸如白蛋白)时,白蛋白会分泌到尿液中,并通常是肾损伤或盐摄入量过多的病征。白蛋白尿还可在患有长期糖尿病(I(1)型或II(2)型糖尿病)的患者中发生。尿白蛋白可通过试纸条测量,或作为在24小时期间采集的总尿液体积中分泌的蛋白量而直接测量。

[0026] 当肾小球对白蛋白有异常高的渗透性,因而肾渗漏少量白蛋白到尿液中时,会出现微量白蛋白尿。当24小时期间的尿白蛋白水平在30mg至300mg的范围内时,则会指示作为糖尿病性肾病病症的微量白蛋白尿。

[0027] 微量白蛋白尿的替代指标是血清中的肌酸酐水平及白蛋白与肌酸酐的比率。白蛋白/肌酸酐比率(ACR)和微量白蛋白尿被定义为ACR≥3.5mg/mmol(女性)或≥2.5mg/mmol(男性),或在两种物质均按质量测量的情况下,被定义为ACR在30μg白蛋白/mg肌酸酐与300μg白蛋白/mg肌酸酐之间。

[0028] 微量白蛋白尿可为肾病的发展及进程的重要预后标志,对于患有糖尿病或高血压的患者而言尤为如此。微量白蛋白尿也是亚临床心血管疾病的指标、血管内皮功能不全的标志以及形成静脉血栓的风险因素。

[0029] 糖尿病性肾病是糖尿病的微血管并发症之一,并且其特征在于白蛋白尿持续存在

以及肾功能逐渐衰退。高血糖是糖尿病性肾病发作及进程推进的重要因素。

[0030] 人们已充分了解患有T1DM(1型糖尿病)的患者中糖尿病性肾病的临床进程的特征。起初,可以观察到过度滤过并伴有肾小球滤过率(GFR)增加以及肾血浆流量升高。元分析发现,患有T1DM的患者若存在过度滤过的病症,则会使微量白蛋白尿或大量白蛋白尿发生的风险增加到两倍以上。该阶段之后出现GFR下降并发生微量白蛋白尿(被定义为≥30mg/天(或20μg/min)且＜300mg/24h(或＜200μg/min)的尿白蛋白分泌),这可伴随血压的升高。之后在疾病进程中,随着GFR继续下降,接着会出现明显的蛋白尿(即,大量白蛋白尿)(被定义为＞300mg/天的尿白蛋白分泌),这与高血压加重相关联。最后,ESKD(终末期肾病)进程推进,从而需要肾替代疗法。

[0031] 对于患有2型糖尿病(T2DM)的患者,临床进程是多变的,主要原因是多发性肾损伤,这不仅包括高血糖,而且包括血管病理,从而导致缺血性肾损伤。然而,其他常见特征可能促使患有T2DM的患者发生肾损伤,包括单个肾单位水平的过度滤过、近端肾小管葡萄糖毒性,以及因钠葡萄糖向肾小管细胞中的增强共转运而对肾小管细胞生长的刺激。

[0032] 研究已证实,白蛋白尿是用于预测糖尿病性肾病进程的生物标志,也是心血管(CV)风险因素。当与具有正常白蛋白尿且估算肾小球滤过率(eGFR)≥90mL/min/1.73m^{2}的患者比较时,具有大量白蛋白尿且eGFR＜60mL/min/1.73m^{2}的患者其心血管死亡的风险是前者的5.9倍(95％CI 3.5至10.2),而经历ESKD的风险是前者的22.2倍(95％CI 7.6至64.7),并且具有大量白蛋白尿和降低的eGFR(即,＜60mL/min/1.73m^2)的受检者有将近6倍经历复合肾事件(即,因肾病而死亡,需要透析或移植,或血清肌酸酐增倍)的可能性。参见例如J Am Soc Nephrol 20(8):1813-1821,2009。还已在RENAAL研究中证实白蛋白尿程度与心血管疾病之间具有紧密联系,表明与ACR＜1.5g/g的患者相比,具有高基线尿白蛋白/肌酸酐比率(ACR)(≥3g/g)的患者并发心肌梗塞(MI)、中风、心力衰竭或不稳定型心绞痛首次住院、冠状血管或外周脉管再通、或心血管死亡的风险是前者的1.2倍(95％CI,1.54至2.38),并且发生心力衰竭的风险是前者的2.7倍(95％CI,1.94至3.75)。尿白蛋白分泌升高和eGFR降低也独立地与患有T2DM的患者中的心血管预后和肾预后两者的风险相关联,但尚无这些风险因素之间相互作用的证据。白蛋白尿适度升高也与肾病进程的加快相关联。

[0033] 概括地说,白蛋白尿的程度与ESKD的发生以及心血管不良预后呈正相关。为患有T2DM和白蛋白尿的患者使用通过血液动力学机制发挥作用的药剂(即,ACEi和ARB)时,该患者的白蛋白尿因治疗而减轻的现象,与糖尿病性肾病进程及心血管不良预后发生率的降低相关联。因此,通过独特血液动力学机制发挥作用使白蛋白尿减少到超过采用其他抗高血压或抗高血糖药剂时所观察到的程度,并对破坏肾素-血管紧张素系统的药剂起到加和效应的药剂,可发挥肾保护作用并可能减少糖尿病性肾病中的心血管不良预后。

[0034] 脂肪肝,也称为脂肪肝病(FLD),是可逆的病症,其中甘油三酯脂肪大液泡经由脂肪变性过程(即,脂质在细胞内的异常滞留)蓄积在肝细胞中。脂肪的蓄积还可伴有肝的进行性炎症(肝炎),这称为脂肪性肝炎。考虑到酒精的促成作用,脂肪肝可称为酒精性脂肪变性或非酒精性脂肪肝病(NAFLD),而更严重的形式称为酒精性脂肪性肝炎(酒精性肝病的一部分)和非酒精性脂肪性肝炎(NASH)。

[0035] 脂肪在肝中沉积(脂肪变性)时会发生脂肪肝,非酒精性脂肪肝病(NAFLD)是出现脂肪肝的病因之一。NAFLD被认为涵盖疾病活动谱。该疾病活动谱一开始是肝中的脂肪蓄积

(肝脂肪变性)。肝可在肝功能未受干扰的情况下保留脂肪,但通过改变机制和对肝的可能损伤,也可进展成NASH,即脂肪变性合并炎症和纤维化的状态。非酒精性脂肪性肝炎(NASH)是NAFLD的渐进性、严重形式。在10年时间内,多达20%的NASH患者会发展成肝硬化,并且10%会因肝病而死亡。NAFLD的确切病因尚属未知,然而,肥胖症和胰岛素抵抗被认为在疾病过程中起着强有力的作用。疾病从一个阶段进展到下一阶段的确切原因和机制是未知的。

[0036] NAFLD与胰岛素抵抗(IR)和代谢综合征(MS)有关。由于肾素-血管紧张素系统(RAS)在胰岛素抵抗中、继而在NAFLD和NASH中起着核心作用,因此已提出将阻断RAS过表达的有害效应的尝试作为治疗靶点。虽然NASH中测试的许多潜在疗法仅靶向该病症的结果,或试图"去除"过多脂肪,但血管紧张素受体阻断剂(ARB)可充当用于修正各种失衡的工具,使之在NASH/NAFLD中发挥协调作用。实际上,通过抑制RAS,可改善细胞内胰岛素信号发送路径,从而更好地控制脂肪组织增殖和脂肪因子生成,并使各种细胞因子的局部水平和系统水平更加均衡。与此同时,通过控制肝中的局部RAS,可预防纤维化并减慢将脂肪变性与坏死性炎症联系起来的周期。(GEORGESCU,E.F.,载于Advances in Therapy,2008,第1141-1174页,第25卷,第11期)。

[0037] 睡眠呼吸暂停是一种睡眠障碍,其特征在于睡眠期间呼吸暂停或者浅呼吸或不频繁呼吸的情况。每次呼吸停止(被称为呼吸暂停)可持续数秒至数分钟,并且根据定义可每小时发生至少5次。相似地,每次异常浅呼吸事件被称为低呼吸。睡眠呼吸暂停被归类为睡眠异常,这是指睡眠期间发生异常行为或心理事件。当呼吸停止时,二氧化碳在血流中堆积。血流中的化学受体注意到高二氧化碳水平。脑发送信号以唤醒睡眠中的人和呼吸空气。呼吸通常将恢复氧水平并且人将再次入睡。睡眠呼吸暂停通常利用过夜睡眠测试或"睡眠研究"来诊断。

[0038] 存在三种形式的睡眠呼吸暂停:中枢型(CSA)、阻塞型(OSA)以及复杂或混合型睡眠呼吸暂停(即,中枢型和阻塞型的组合),其分别构成情形的0.4%、84%和15%。在CSA中,呼吸由于缺乏呼吸用力而中断。在OSA中,虽然呼吸用力,但呼吸由于物理阻塞气流而中断,并且打鼾是常见的。根据NIH,1200万美国人具有OSA。因为人们未报告病症或不知道他们具有睡眠呼吸暂停,所以还存在更多睡眠呼吸暂停的情况。

[0039] 无论何种类型,具有睡眠呼吸暂停的个体甚至在被叫醒时也很少意识到难以呼吸。睡眠呼吸暂停通过在发作期间他人对个体的目击而被认为是一个问题,或者由于其对身体的影响而受到怀疑。症状可在未识别的情况下存在数年(或甚至数十年),期间,个人可变得习惯于与睡眠干扰相关的白天嗜睡和疲劳。睡眠呼吸暂停不仅影响成人而且也影响一些儿童。

[0040] 睡眠呼吸暂停的症状包括过度白天嗜睡(EDS)和警觉性受损。换句话讲,睡眠呼吸暂停的常见效应包括白天疲劳、反应时间较慢、和视觉问题。OSA可增加驾驶意外和工作相关的意外的风险。如果不治疗OSA,则患者具有增加的其它健康问题(诸如糖尿病)的风险。甚至由于身体缺氧,由于未治疗的OSA可发生死亡。此外,使用"标准测试组合"检查患有睡眠呼吸暂停的人,以便进一步识别脑中可受睡眠呼吸暂停不利影响的部分,包括支配下列的那些:"执行功能",人计划并启动工作的方式;在清醒状态下,注意力、有效工作和处理信息;使用记忆和学习。由于白天认知状态的干扰,也存在行为效应。这些包括情绪化、好战

性、以及注意力和内驱力下降。睡眠呼吸暂停的另一症状是睡眠麻痹中的唤醒。在严重的情况下，由于睡眠麻痹的睡眠恐惧可导致失眠。这些效应变得非常难以处理，因此抑郁症的发展可能发生。

[0041] 有证据表明，中度或重度睡眠呼吸暂停患者发生糖尿病的风险较高。越来越多的证据表明睡眠呼吸暂停也可能导致肝功能障碍，特别是脂肪肝疾病。

[0042] 无论性别、种族或年龄，睡眠呼吸暂停均可影响人们。风险因素包括男性、超重、肥胖或超过40岁；或具有大的颈部尺寸(大于16—17英寸)、扁桃体肿大、舌部肿大、颌骨小、胃食道回流、过敏症、窦问题、睡眠呼吸暂停的家族史、或导致鼻堵塞的鼻中隔偏转。酒精、镇静剂和安神药也由于使喉部松弛而促进睡眠呼吸暂停。吸烟者具有睡眠呼吸暂停的比率是从不抽烟者的三倍。上述所有因素均可有助于阻塞性睡眠呼吸暂停。中枢型睡眠呼吸暂停更多受下列影响：男性、大于65岁，具有心脏病诸如心房颤动、和中风或脑肿瘤。脑肿瘤可阻碍脑调节正常呼吸的能力。高血压在患有睡眠呼吸暂停者中也是非常常见的。

[0043] 在成人中，OSA的最常见原因是过重和肥胖症，这与嘴部和喉部的软组织相关。在睡眠期间，当喉部与舌部肌肉更松弛时，该软组织可导致气道被阻塞。在儿童中，OSA的原因通常包括扁桃体肿大或腺状肿大、以及牙齿病症诸如龅牙。较不常见的原因包括气道中的肿瘤或增生，以及出生缺陷诸如唐氏综合征和皮埃尔-罗宾综合征。虽然儿童期肥胖症可导致OSA，但与成人肥胖症相比，其与病症的相关性通常小得多。

[0044] 就许多患有睡眠障碍(包括睡眠呼吸暂停)的患者而言，第一且最佳治疗是体重减轻。尽管不是每个患有睡眠呼吸暂停者均是超重的，但大多数患者是超重的，并且理论上减重有助于消除阻断气管，从而导致睡眠呼吸暂停的脂肪。

[0045] 在许多物种(包括酵母、蠕虫、飞虫、啮齿类、猴和可能的人)中，卡路里限制(CR)增加寿命并且减慢年龄相关退化变化。卡路里限制影响调节关键细胞功能的某些信号发送路径，包括胰岛素/胰岛素样生长因子-1路径、营养素反应“雷帕霉素靶蛋白(TOR)”路径、以及蛋白质脱乙酰酶的活性。某些蛋白质脱乙酰酶调节组蛋白的DNA-结合活性，这继而调节特定基因的转录和表达，因此影响细胞和器官功能。

[0046] 卡路里限制，如空腹，触发储存的脂肪储备作为能源使用。脂肪氧化导致酮体(小代谢物，诸如乙酰乙酸酯和β-羟基丁酸酯(BOHB))的循环水平升高，当葡萄糖水平降低时，这被用作一些组织诸如大脑的替代能源(NEWMAN,J.C.等人,Ketone bodies as signaling metabolites,Trends Endocrinology and Metabolism,2014,第1期,第25卷第42页)。

[0047] 目前公布的数据指示BOHB不仅是替代的代谢燃料，而且意料不到的还具有特定细胞信号发送和调节作用；这些作用可介导与卡路里限制相关的某些长寿促进效应。具体地讲，BOHB已经示出直接抑制某些组蛋白脱乙酰酶(HDAC)，并且经培养细胞的BOHB处理增加组蛋白乙酰化，类似于在动物中在空腹时观察到的(SHIMAZU,T.等人,Suppression of Oxidative Stress by Beta-Hydroxybutyrate,an Endogenous Histone Deacetylase Inhibitor,Science,2013,第339卷第211页)。小鼠的BOHB处理增加了组蛋白乙酰化，从而改变了与抗氧化应激反应性相关的某些基因的表达，值得注意的是FOXO3基因，其是转录因子DAF16(是蠕虫寿命的关键调节子)的哺乳动物型式。由BOHB抑制HDAC也可调节非组蛋白的乙酰化状态和活性，所述非组蛋白也具有细胞保护效应。

[0048] 目前，报道了BOHB抑制NLRP3炎症小体，其是一种先天免疫系统的感应器，其通常

触发对多种有害试剂，诸如过量葡萄糖、尿酸盐和与一些慢性疾病相关的淀粉蛋白的炎性反应。空腹或产酮饮食的已知抗炎性效应已经归因于BOHB的这种效应(YOUM,Y.H.等人,The ketone metabolite beta-hydroxybutyrate blocks NLRP3mflammasome-mediated inflammatory disease,Nature Medicine,2015,第3期,第21卷,第263页)。

[0049] 公布的数据还指示BOHB结合到两种特定细胞表面受体(GPR109和GPR41;TAGGART,A.K.等人,D-Beta-Hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMB-G,J.Biol.Chem.,2005,第280卷,第26649页;和KIMURA,I.等人,Short-chain fatty acids and ketones directly regulate sympathetic nervous system via GPR41,Proc.Natl.Acad.Sci.USA,2011,第108卷,第8030页)。在小鼠中，结合到GPR41(一种在交感神经元中表达的G蛋白质偶联受体)的BOHB抑制交感神经活性，减少脂肪氧化，并降低总体代谢率。在蠕虫(秀丽隐杆线虫(C.elegans))中，BOHB处理被报道增加寿命约20％(EDWARDS,C.等人,D-Beta-Hydroxybutyrate extends lifespan in C.elegans,Aging,2014,第8期,第6卷,第621页)。

[0050] 空腹不是提升酮体水平的唯一方法。产酮饮食(其减少碳水化合物摄入)也增加BOHB循环水平。动物中的产酮饮食引发许多生物化学变化，所述生物化学变化与保护细胞免受氧化应激反应相关联并且与增加的寿命相关联。

[0051] 糖尿病患者的卡格列净治疗(通过抑制肾SGLT2活性)诱发糖尿，这导致储存的脂肪储备的利用增加(导致肥胖症减轻和体重减轻)。类似于空腹和产酮饮食，糖尿病患者的卡格列净治疗也诱发酮体(包括BOBH)循环水平的增加。

[0052] 仍然需要提供对肥胖症和肥胖症相关疾病(包括由于肥胖症，或由肥胖症恶化和/或由肥胖症加速的障碍、疾病和病症)的有效治疗。

发明内容

[0053] 本发明涉及一种用于治疗、延迟、减慢肥胖症和肥胖症相关疾病进程和/或预防肥胖症和肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0054] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0055] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0056] 本发明涉及一种用于治疗肥胖症、促进体重减轻和/或抑制食欲的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0057] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0058] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0059] 本发明涉及一种用于减少食物摄取、引起饱腹感或控制体重增加的方法，所述方

法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0060] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0061] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0062] 在某些实施方案中，本发明涉及一种用于长期体重管理的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0063] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0064] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0065] 在某些实施方案中，本发明涉及用于治疗肥胖症、促进体重减轻、抑制食欲、减少食物摄取、引起饱腹感和/或控制体重增加的方法，所述方法包括通过测定受检者的身体质量指数(BMI)来识别对其有需要的受检者；并且其中受检者的身体质量指数大于或等于约25kg/m^2(优选地大于或等于约30kg/m^2)，施用治疗有效量的协同治疗，所述协同治疗包含：

[0066] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0067] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0068] 本发明还涉及一种体重减轻的方法、一种治疗肥胖症的方法、或一种治疗肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0069] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0070] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0071] 更优选地，并且其中在26周之后达到的体重减轻量为约5％，优选地约7.5％。

[0072] 在一个实施方案中，本发明涉及一种体重减轻的方法、一种治疗肥胖症的方法、或一种治疗肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含如本文所述的卡格列净和芬特明，其中在约26周内，受检者达到或经历在约5％至约10％范围内，或其中的任何量或范围的体重减轻，优选地至少约5％的体重减轻，更优选地至少约7.5％的体重减轻。

[0073] 在另一个实施方案中，本发明涉及一种体重减轻的方法、一种治疗肥胖症的方法、或一种治疗肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含如本文所述的卡格列净和芬特明，其中在介于约26周和约

104周之间的时间段内，优选地在约26周和约52周的时间段内，受检者达到或经历在约5％至约10％范围内，或其中的任何量或范围的体重减轻，优选地至少约5％的体重减轻，更优选地至少约7.5％的体重减轻。

[0074] 在另一个实施方案中，本发明涉及一种体重减轻的方法、一种治疗肥胖症的方法、或一种治疗肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含如本文所述的卡格列净和芬特明，其中所述协同治疗结合饮食和运动咨询一起施用。在另一个实施方案中，本发明涉及一种体重减轻的方法、一种治疗肥胖症的方法、或一种治疗肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用协同治疗，所述协同治疗包含如本文所述的卡格列净和芬特明，其中所述协同治疗结合饮食和运动计划一起施用。在本发明的某些实施方案中，饮食和运动咨询或者饮食和运动计划包括：(a)建议受检者增加身体活动，(b)建议受检者降低膳食脂肪含量和/或(c)建议受检者消耗更多卡路里。在某些实施方案中，本发明涉及用于长期体重管理的方法，所述方法包括对其有需要的受检者施用协同治疗，所述协同治疗包含如本文所述的卡格列净和芬特明，优选地其中所述协同治疗是低卡路里饮食和增加身体活动的助剂。

[0075] 在本发明的某些实施方案中，对其有需要的受检者是其测定的(例如，测量的)身体质量指数(BMI)大于或等于约23kg/m^2的受检者(成人或儿童)。在本发明的某些附加实施方案中，对其有需要的受检者是其测定的(例如，测量的)身体质量指数大于或等于约25kg/m^2的受检者(成人或儿童)。在本发明的某些附加实施方案中，对其有需要的受检者是其测定的(例如，测量的)身体质量指数大于或等于约30kg/m^2的受检者(成人或儿童)。在本发明的某些附加实施方案中，对其有需要的受检者是其测定的(例如，测量的)身体质量指数大于或等于约35kg/m^2的受检者(成人或儿童)。在本发明的某些附加实施方案中，对其有需要的受检者是其测定的(例如，测量的)身体质量指数在约23kg/m^2至约29.9kg/m^2范围内的受检者(成人或儿童)。

[0076] 在本发明的某些实施方案中，对其有需要的受检者是其测定的(例如，测量的)身体质量指数大于或等于约23kg/m^2，优选地大于或等于约25kg/m^2，更优选地大于或等于约30kg/m^2，更优选地大于或等于约40kg/m^2的受检者(成人或儿童)，并且受检者被诊断患有或表现出选自下列的共病病症的至少一种症状：糖尿病前期、口服葡萄糖耐量受损、II型糖尿病、代谢综合征(也被称为X综合征)、心血管风险因素、肾或脂肪肝疾病(包括但不限于NASH、NAFLD等)、睡眠呼吸暂停等。在另一实施方案中，共病病症选自：糖尿病前期、口服葡萄糖耐量受损、II型糖尿病和代谢综合征(也被称为X综合征)。在另一实施方案中，共病病症选自：心血管风险因素、以及肾或脂肪肝疾病(包括但不限于NASH、NAFLD等)。

[0077] 在本发明的某些实施方案中，对其有需要的受检者为以下受检者：初始身体质量指数大于或等于约30kg/m^2；或者大于或等于约27kg/m^2，并且诊断患有或表现出至少一种体重相关共病病症(诸如，例如，高血压、血脂异常、糖尿病前期或II型糖尿病)。

[0078] 在本发明的某些实施方案中，对其有需要的受检者为其腰臀比大于或等于1.0(如果受检者是男性)或者大于或等于约0.8(如果受检者是女性)的受检者。在本发明的某些附加实施方案中，对其有需要的受检者为其腰围＞40英寸或102cm(如果受检者是男性)或者＞35英寸或94cm(如果受检者是女性)的受检者。

[0079] 在本发明的某些实施方案中，对其有需要的受检者为其体脂含量大于约25％，优

选地大于约30％的受检者。在本发明的某些附加实施方案中，对其有需要的受检者为其体脂含量大于约25％(如果受检者是男性)或者大于约30％(如果受检者是女性)的受检者。

[0080] 在某些实施方案中，本发明涉及用于治疗对其有需要的受检者的肥胖症、促进体重减轻、抑制食欲、减少食物摄取、引起饱腹感和/或控制体重增加的方法，其中对其有需要的受检者为减肥手术的候选者或已经经过减肥手术(包括胃旁路术手术、胃/胃部束带手术等)的受检者。

[0081] 在某些实施方案中，本发明涉及用于治疗对其有需要的受检者的肥胖症、促进体重减轻、抑制食欲、减少食物摄取、引起饱腹感和/或控制体重增加的方法，其中对其有需要的受检者是体重减轻促进医疗装置的候选者或已经植入体重减轻促进医疗装置(例如，腔内套管、胃内球囊、减少或再分配受检者的胃肠内腔容积的装置、输送电流以刺激胃或消化道的其它神经的装置，输送电荷以抑制通向胃的迷走神经的装置、脑部深层刺激装置、将电荷输送至经由运动来激活的神经系统的部分的装置等)。

[0082] 在一个实施方案中，本发明涉及一种治疗肥胖症的方法，所述方法包括向对其有需要的受检者施用治疗有效量的如本文所述的任何协同治疗。在另一个实施方案中，本发明涉及一种促进体重减轻的方法，所述方法包括向对其有需要的受检者施用治疗有效量的如本文所述的协同治疗。在另一个实施方案中，本发明涉及一种抑制食欲的方法，所述方法包括向对其有需要的受检者施用治疗有效量的如本文所述的协同治疗。在另一个实施方案中，本发明涉及一种减少食物摄取的方法，所述方法包括向对其有需要的受检者施用治疗有效量的如本文所述的协同治疗。在另一个实施方案中，本发明涉及一种引起饱腹感的方法，所述方法包括向对其有需要的受检者施用治疗有效量的如本文所述的协同治疗。在另一个实施方案中，本发明涉及一种控制重量增加的方法，所述方法包括向对其有需要的受检者施用治疗有效量的如本文所述的协同治疗。

[0083] 在一个实施方案中，本发明涉及用于治疗肥胖症、促进体重减轻、抑制食欲、减少食品摄取、引起饱腹感和/或控制体重增加的方法，其中对其有需要的受检者具有大于约25kg/m^2的测量BMI，并且其具有选自下列的一种或多种共病(或共存)病症：糖尿病前期、口服葡萄糖耐量受损、II型糖尿病、代谢综合征(也被称为X综合征)、心血管风险因素、肾或脂肪肝疾病(包括但不限于NASH、NAFLD等)和睡眠呼吸暂停。

[0084] 在另一个实施方案中，本发明涉及用于治疗肥胖症、促进体重减轻、抑制食欲、减少食品摄取、引起饱腹感和/或控制体重减轻的方法，其中对其有需要的受检者具有大于约25kg/m^2的测量BMI，并且其具有选自下列的一种或多种共病(或共存)病症：糖尿病前期、口服葡萄糖耐量受损、II型糖尿病、和代谢综合征(也被称为X综合征)。在另一个实施方案中，本发明涉及用于治疗肥胖症、促进体重减轻、抑制食欲、减少食品摄取、引起饱腹感和/或控制体重减轻的方法，其中对其有需要的受检者具有大于约25kg/m^2的测量BMI，并且其具有选自下列的一种或多种共病(或共存)病症：心血管风险因素以及肾或脂肪肝疾病(包括但不限于NASH、NAFLD等)。

[0085] 本发明还涉及用于治疗、延迟、减慢代谢紊乱的进程和/或预防代谢紊乱的方法(包括但不限于高血糖、糖尿病前期、口服葡萄糖耐量受损、空腹血液葡萄糖受损、餐后高血糖、高胰岛素血症、胰岛素抵抗、2型糖尿病(包括但不限于晚期2型糖尿病)、1型糖尿病、MODY、LADA、NODAT、妊娠期糖尿病、血糖控制不足(或血糖控制不充分)和代谢综合征(也被

称为X综合征)，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0086] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0087] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0088] 在本发明的一些实施方案中，所述代谢紊乱选自：糖尿病前期、口服葡萄糖耐量受损、空腹血液葡萄糖受损、胰岛素抵抗、2型糖尿病和X综合征。在本发明的另一个实施方案中，代谢紊乱选自：1型糖尿病、2型糖尿病、青春晚期糖尿病(MODY)、成人隐匿性自身免疫性糖尿病(LADA)和糖尿病前期。

[0089] 在本发明的一些实施方案中，对其有需要的受检者经诊断患有或表现出以下一种或多种病症的症状：1型糖尿病、2型糖尿病、青春晚期糖尿病(MODY)、成人隐匿性自身免疫性糖尿病(LADA)和糖尿病前期。在本发明的另一个实施方案中，对其有需要的受检者经诊断患有或表现出2型糖尿病和/或糖尿病性肾病的症状。在本发明的另一个实施方案中，对其有需要的受检者经诊断患有或表现出2型糖尿病和/或血糖控制不足的症状。

[0090] 在本发明的另一个实施方案中，有需要的受检者是：

[0091] (1)诊断出患有选自下列的病症中一种或多种的个体：超重、肥胖症、内脏型肥胖症和腹部肥胖症；或者

[0092] (2)表现出以下病征中的一种、两种或更多种的个体：

[0093] (a)空腹血液葡萄糖或血清葡萄糖浓度大于约100mg/dL，尤其是大于约125mg/dL；

[0094] (b)餐后血浆葡萄糖等于或大于约140mg/dL；

[0095] (c)HbA1c值等于或大于约7.0％；

[0096] (3)存在以下病症中的一种、两种、三种或更多种的个体：

[0097] (a)肥胖症、内脏型肥胖症和/或腹部肥胖症，

[0098] (b)血液甘油三酯水平等于或大于约150mg/dL，

[0099] (c)女性患者的血液HDL-胆固醇水平小于约40mg/dL，以及男性患者的血液HDL-胆固醇水平小于约50mg/dL，

[0100] (d)收缩压等于或大于约130mmHg，以及舒张压等于或大于约85mmHg，

[0101] (e)空腹血液葡萄糖水平等于或大于约100mg/dL；或者

[0102] (4)患有肥胖症的个体。

[0103] 在一个实施方案中，本发明涉及用于预防、减慢2型糖尿病的发展或减慢2型糖尿病的进程的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0104] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0105] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0106] 本发明还涉及一种用于提供心血管保护的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0107] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0108] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0109] 本发明还涉及用于预防主要不良心脏事件(MACE)的方法(例如，心肌梗塞、不稳定型心绞痛、心血管死亡、脉管再通、致命或非致命脑血管意外、外周动脉病、主动脉事件和由于充血性心力衰竭的住院)，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0110] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0111] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0112] 本发明还涉及用于治疗、延迟、减慢心血管事件的进程和/或预防心血管事件的方法(包括主要不良心脏事件(MACE)诸如心肌梗塞、不稳定型心绞痛、心血管死亡、脉管再通、致命或非致命脑血管意外、外周动脉病、主动脉事件和由于充血性心力衰竭的住院等)；所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0113] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以100mg或约300mg的量)施用；以及

[0114] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0115] 在本发明的一个实施方案中，MACE或心血管事件选自：心肌梗塞、不稳定型心绞痛、心血管死亡、脉管再通、致命或非致命脑血管意外(例如，中风)、外周动脉病、主动脉事件和由于充血性心力衰竭的住院。在本发明的另一个实施方案中，心血管事件选自：心肌梗塞、致命或非致命脑血管意外(例如，中风)或由于充血性心力衰竭的住院。在本发明的另一个实施方案中，MACE或心血管事件为心肌梗塞或致命或非致命脑血管意外(例如，中风)。在本发明的另一个实施方案中，MACE或心血管事件为致命或非致命脑血管意外(例如，中风)。在本发明的另一个实施方案中，MACE或心血管事件为心肌梗塞。

[0116] 在一个实施方案中，本发明涉及降低血压，优选地降低收缩压的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0117] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0118] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0119] 本发明还涉及用于治疗、延迟、减慢肾或脂肪肝疾病的进程和/或预防肾或脂肪肝疾病的方法(所述肾或脂肪肝疾病包括但不限于NASH、NAFLD等),所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

[0120] (a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量,更优选地以约100mg的量或约300mg的量)施用;以及

[0121] (b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量,更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0122] 在本发明的一个实施方案中,所述肾或脂肪肝疾病选自:酒精性单纯性脂肪肝、酒精性脂肪性肝炎(ASH)、酒精性肝纤维化、酒精性肝硬化、非酒精性脂肪肝病(NAFLD)、非酒精性单纯性脂肪肝、非酒精性脂肪性肝炎(NASH)、非酒精性肝纤维化和非酒精性肝硬化。在本发明的另一个实施方案中,所述肾或脂肪肝疾病选自:非酒精性脂肪肝病(NAFLD)、非酒精性单纯性脂肪肝、非酒精性脂肪性肝炎(NASH)、非酒精性肝纤维化和非酒精性肝硬化。在本发明的另一个实施方案中,所述肾或脂肪肝疾病选自:NAFLD和NASH。在本发明的另一个实施方案中,所述肾疾病为糖尿病性肾病。

[0123] 在本发明的另一个实施方案中,所述肾或脂肪肝疾病选自:过度滤过性糖尿病性肾病、肾过度滤过、肾小球过度滤过、肾同种异体移植过度滤过、代偿性过度滤过、过度滤过性慢性肾病和过度滤过性急性肾衰竭。在本发明的另一个实施方案中,所述肾疾病选自:微量白蛋白尿、大量白蛋白尿、高尿白蛋白水平和高白蛋白/肌酸酐比率(ACR)。

[0124] 本发明还涉及用于下列的方法:(a)治疗、延迟、减慢微量白蛋白尿的进程、诱发微量白蛋白尿的缓解或预防微量白蛋白尿(尿白蛋白水平升高);(b)治疗、延迟、减慢大量白蛋白尿的进程、或预防大量白蛋白尿;(c)降低尿白蛋白水平;和/或(d)降低白蛋白/肌酸酐比率(ACR);所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

[0125] (a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量,更优选地以约100mg的量或约300mg的量)施用;以及

[0126] (b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量,更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0127] 本发明还涉及用于预防、减慢过度滤过性肾损伤的进程、延迟和/或治疗过度滤过性肾损伤的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

[0128] (a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量,更优选地以约100mg的量或约300mg的量)施用;以及

[0129] (b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量,更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0130] 本发明还涉及用于预防、减慢选自下列的病症或疾病的进程、延迟或治疗选自下列的病症或疾病的方法:过度滤过性糖尿病性肾病、肾过度滤过、肾小球过度滤过、肾同种

异体移植过度滤过、代偿性过度滤过(例如通过手术肾质量减少后)、过度滤过性慢性肾病、过度滤过性急性肾衰竭、和肥胖症,所述方法包括向对其有需要的受检者施用协同治疗,所述协同治疗包含:

[0131] (a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量,更优选地以约100mg的量或约300mg的量)施用;以及

[0132] (b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量,更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0133] 本发明还涉及用治疗、延迟、减慢糖尿病性神经性病变的进程、和/或预防糖尿病性神经性病变的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

[0134] (a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量,更优选地以约100mg的量或约300mg的量)施用;以及

[0135] (b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量,更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0136] 在本发明的一个实施方案中,对其有需要的受检者经诊断患有或表现出以下一种或多种病症的症状:

[0137] (a)糖尿病,无论何种类型;

[0138] (b)慢性肾病(CKD);

[0139] (c)急性肾衰竭(ARF);

[0140] (d)肾移植受者;

[0141] (e)肾移植供者;或者

[0142] (f)单侧肾全部或部分切除的患者;或者

[0143] (g)肾病综合征。

[0144] 本发明还涉及用于治疗或预防睡眠障碍的方法(包括但不限于睡眠呼吸障碍等),所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:

[0145] (a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量,更优选地以约100mg的量或约300mg的量)施用;以及

[0146] (b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量,更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0147] 本发明还涉及用于延长受检者的生命或寿命的方法,所述方法包括向受检者施用协同治疗,所述协同治疗包含:

[0148] (a)卡格列净;其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量,更优选地以约100mg的量或约300mg的量)施用;以及

[0149] (b)芬特明;其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量,更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0150] 本发明还涉及用于治疗肥胖症、促进体重减轻、抑制食欲、减少食物摄取、引起饱腹感和/或控制体重增加的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0151] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0152] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0153] 其中，对其有需要的受检者是服用一种或多种其潜在副作用包括体重增加的药剂(药物)的受检者。

[0154] 本发明还涉及治疗、延迟、减慢选自下列的疾病的进程和/或预防选自下列的疾病的方法：呼吸急促、胆囊疾病、癌症(例如，子宫内膜癌、乳腺癌、前列腺癌、结肠癌)、骨关节炎、矫形问题、逆流性食道炎(胃灼热)、打鼾、多囊卵巢综合征、压力性失禁、月经不规律、不育症、心脏病、抑郁症、焦虑症、痛风、β-细胞功能障碍、低呼吸，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0155] (a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约100mg至约300mg范围内的量，更优选地以约100mg的量或约300mg的量)施用；以及

[0156] (b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0157] 在一个实施方案中，本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：(a)卡格列净；其中所述卡格列净以每天约100mg的量施用；以及(b)芬特明；其中所述芬特明以每天约3.75mg的量施用。

[0158] 在一个实施方案中，本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：(a)卡格列净；其中所述卡格列净以每天约100mg的量施用；以及(b)芬特明；其中所述芬特明以每天约7.5mg的量施用。

[0159] 在一个实施方案中，本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：(a)卡格列净；其中所述卡格列净以每天约100mg的量施用；以及(b)芬特明；其中所述芬特明以每天约15mg的量施用。

[0160] 在一个实施方案中，本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：(a)卡格列净；其中所述卡格列净以每天约100mg的量施用；以及(b)芬特明；其中所述芬特明以每天约30mg的量施周。

[0161] 在一个实施方案中，本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：(a)卡格列净；其中所述卡格列净以每天约100mg的量

施用;以及(b)芬特明;其中所述芬特明以每天约37.5mg的量施用。

[0162] 在一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明以每天约3.75mg的量施用。

[0163] 在一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明以每天约7.5mg的量施用。

[0164] 在一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明以每天约15mg的量施周。

[0165] 在一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明以每天约30mg的量施用。

[0166] 在一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明以每天约37.5mg的量施用。

[0167] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约100mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约3.75mg的量施用。

[0168] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约100mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约7.5mg的量施用。

[0169] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约100mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约15mg的量施用。

[0170] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;

并且其中所述卡格列净以每天约100mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约30mg的量施用。

[0171] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病的进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约100mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约37.5mg的量施用。

[0172] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病的进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约3.75mg的量施用。

[0173] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约7.5mg的量施用。

[0174] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病的进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约15mg的量施用。

[0175] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约30mg的量施用。

[0176] 在另一个实施方案中,本发明涉及治疗、延迟、减慢肥胖症和肥胖症相关疾病进程或者预防肥胖症和肥胖症相关疾病的方法,所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗,所述协同治疗包含:(a)卡格列净;其中所述卡格列净是结晶半水合物;并且其中所述卡格列净以每天约300mg的量施用;以及(b)芬特明;其中所述芬特明为芬特明盐酸盐,并且其中所述芬特明以每天约37.5mg的量施用。

[0177] 在本发明的某些实施方案中,卡格列净是结晶的卡格列净半水合物。在本发明的某些实施方案中,芬特明是芬特明盐酸盐。

[0178] 在本发明的一个实施方案中,卡格列净以约50mg至约500mg范围内的量施用。在本发明的另一个实施方案中,卡格列净以约100mg至约300mg范围内的量施用。在本发明的另一个实施方案中,卡格列净以约100mg的量施用。在本发明的另一个实施方案中,卡格列净以约300mg的量施用。

[0179] 在本发明的一个实施方案中,芬特明以在约3.75mg至约50mg范围内的量施用。在

本发明的另一个实施方案中，芬特明以在约3.75mg至约37.5mg范围内的量施用。在本发明的另一个实施方案中，芬特明以在约7.5mg至约37.5mg范围内的量施用。在本发明的另一个实施方案中，芬特明以在约7.5mg至约15mg范围内的量施用。在本发明的另一个实施方案中，芬特明以约3.75mg的量施用。在本发明的另一个实施方案中，芬特明以约7.5mg的量施用。在本发明的另一个实施方案中，芬特明以约15mg的量施用。在本发明的另一个实施方案中，芬特明以约30mg的量施用。在本发明的另一个实施方案中，芬特明以约37.5mg的量施用。

[0180] 在本发明的另一个实施方案中，芬特明以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量施用。在本发明的另一个实施方案中，芬特明以约3.75mg、约7.5mg或约15mg的量施用。在本发明的另一个实施方案中，芬特明以约7.5mg或约15mg的量施用。

[0181] 在一个实施方案中，协同治疗包含约100mg的量的卡格列净和约3.75mg的量的芬特明，每天至少施用一次(优选地每天一次)。在另一个实施方案中，协同治疗包含约100mg的量的卡格列净和约7.5mg的量的芬特明，每天至少施用一次(优选地每天一次)。在一个实施方案中，协同治疗包含约100mg的量的卡格列净和约15mg的量的芬特明，每天至少施用一次(优选地每天一次)。在一个实施方案中，协同治疗包含约100mg的量的卡格列净和约30mg的量的芬特明，每天至少施用一次(优选地每天一次)。在一个实施方案中，协同治疗包含约100mg的量的卡格列净和约37.5mg的量的芬特明，每天至少施用一次(优选地每天一次)。

[0182] 在一个实施方案中，协同治疗包含约300mg的量的卡格列净和约3.75mg的量的芬特明，每天至少施用一次(优选地每天一次)。在另一个实施方案中，协同治疗包含约300mg的量的卡格列净和约7.5mg的量的芬特明，每天至少施用一次(优选地每天一次)。在一个实施方案中，协同治疗包含约300mg的量的卡格列净和约15mg的量的芬特明，每天至少施用一次(优选地每天一次)。在一个实施方案中，协同治疗包含约300mg的量的卡格列净和约30mg的量的芬特明，每天至少施用一次(优选地每天一次)。在一个实施方案中，协同治疗包含约300mg的量的卡格列净和约37.5mg的量的芬特明，每天至少施用一次(优选地每天一次)。

[0183] 本发明的示例为一种药物组合物，其包含：(a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约50mg至约300mg范围内的量，更优选地以约50mg、约100mg或约300mg的量)施用；(b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用；以及(c)药学上可接受的载体。

[0184] 本发明的示例为一种药物组合物，其通过将以下物质混合来制备：(a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约50mg至约300mg范围内的量，更优选地以约50mg、约100mg或约300mg的量)施用；(b)芬特明；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约37.5mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用；以及(c)药学上可接受的载体。本发明的一个示例是用于制备药物组合物的方法，该方法包括将根据本文所述的方法制备的产物与药学上可接受的载体混合。

[0185] 本发明例举了用于治疗、延迟、减慢肥胖症和肥胖症相关疾病的进程和/或预防肥胖症和肥胖症相关疾病的方法，所述方法包括向对其有需要的受检者施用治疗有效量的本文所述药物组合物中的任一种。

[0186] 在另一个实施方案中，本发明涉及一种用于治疗、延迟、减慢肥胖症或肥胖症相关疾病的进程和/或预防肥胖症或肥胖症相关疾病的组合物，所述组合物包含：(a)卡格列净；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在50mg至约300mg范围内的量，更优选地以约50mg、约100mg或约300mg的量)施用；(b)芬特明；其中所述芬特明以每天约37.5mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用；以及(c)药学上可接受的载体。

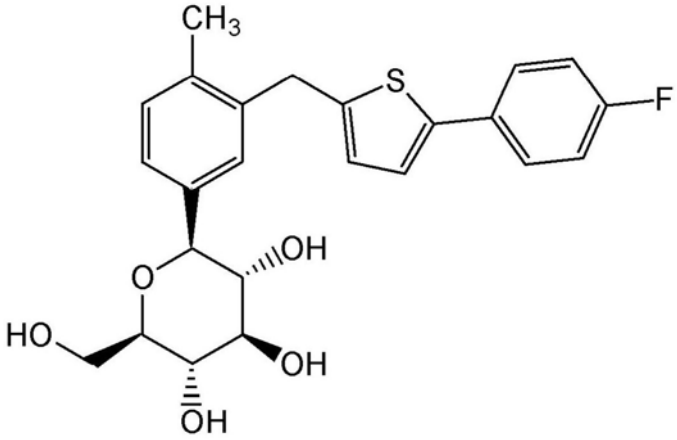
具体实施方式

[0187] 本发明涉及用于治疗、延迟、减慢肥胖症和肥胖症相关疾病的进程和/或预防肥胖症和肥胖症相关疾病的方法(所述疾病包括代谢紊乱如糖尿病前期、2型糖尿病、X综合征等，肾或脂肪肝疾病诸如NASH、NAFLD等，心血管事件(或MACE)、睡眠呼吸暂停等)，所述方法包括向对其有需要的受检者施用治疗有效量的协同治疗，所述协同治疗包含：

[0188] (a)卡格列净(优选地卡格列净的结晶半水合物形式)；其中所述卡格列净以每天约50mg至约500mg范围内的量(优选地以在约50mg至约300mg范围内的量，更优选地以约50mg、约100mg或约300mg的量)施用；以及

[0189] (b)芬特明(优选地芬特明盐酸盐)；其中所述芬特明以每天约3.75mg至约50mg范围内的量(优选地以在约3.75mg至约37.5mg范围内的量，更优选地以约3.75mg、约7.5mg、约15mg、约30mg或约37.5mg的量)施用。

[0190] 如本文所用，除非另外指明，否则术语“卡格列净”应指式(I-X)的化合物；

[0191] 

(I-X)

[0192] 也被称为(1S)-1,5-无水-1-[3-[[5-(4-氟苯基)-2-噻吩基]甲基]-4-甲基苯基]-D-葡萄糖醇，或式(I-X)的化合物的结晶半水合物形式。式(I-X)的化合物表现出对诸如例如SGLT2的钠依赖型葡萄糖转运蛋白的抑制活性；并且可根据Nomura,S.等人在美国专利公布US 2005/0233988 A1中所公开的方法来制备，该专利公布于2005年10月20日，其以引用方式并入本文。

[0193] 如本文所用，术语“卡格列净”还应包括立体异构体的混合物，或各自纯的或基本上纯的异构体。另外，术语“卡格列净”应包括其分子内盐、水合物、溶剂化物或多晶型物。在某些实施方案中，术语“卡格列净”应指式(I-X)化合物的结晶半水合物形式，如WO 2008/069327中所述，该专利的公开内容据此全文以引用方式并入本文。

[0194] 如本文所用,术语“芬特明”应指2-甲基-1-苯基丙-2-胺,及其药学上可接受的盐,优选地芬特明盐酸盐。芬特明是拟交感神经胺减食欲药,其指示为肥胖症管理中的体重减轻方案(包括运动、行为修改和卡路里限制)中的短期助剂。芬特明被批准作为食欲抑制剂并且在医学上指定为减肥药;其旨在用于肥胖患者和被认为是由于体重导致医学风险的患者。存在各种芬特明品牌以及补充剂,其可通过片剂、胶囊和饮料获得,包括VITES、ADIPED、ADIPEX-P、SUPRENZA、IONAMIN和QSYMIA(与托吡酯的协同治疗),其以各种剂量可用,包括15mg、30mg和37.5mg。

[0195] 在某些实施方案中,芬特明的剂量(以mg计)应当是指施用于或存在于药物组合物中的芬特明游离碱或游离碱等同物的量(当芬特明以其药学上可接受的盐存在,例如以芬特明盐酸盐形式存在时)。

[0196] 人类患者的术语“身体质量指数”或“BMI”被定义为体重(以千克计)除以身高(以米计)的平方,因此BMI的单位为kg/m^2。术语“超重”被定义为其中欧裔成年个体的BMI等于或大于$25kg/m^2$且小于$30kg/m^2$的病症。对于亚裔受检者,术语“超重”被定义为其中成年个体的BMI等于或大于$23kg/m^2$且小于$25kg/m^2$的病症。术语“超重”和“肥胖前期”可互换使用。

[0197] 术语“肥胖症”被定义为欧裔成年个体的BMI等于或大于$30kg/m^2$的病症。根据WHO定义,术语肥胖症可如下分类:术语“I类肥胖症”是其中BMI等于或大于$30kg/m^2$但低于$35kg/m^2$的病症;术语“II类肥胖症”是其中BMI等于或大于$35kg/m^2$但低于$40kg/m^2$的病症;术语“III类肥胖症”是其中BMI等于或大于$40kg/m^2$的病症。对于亚裔受检者,术语“肥胖症”被定义为成年个体的BMI等于或大于$25kg/m^2$的病症。亚洲人的肥胖症可进一步如下分类:术语“I类肥胖症”是其中BMI等于或大于$25kg/m^2$但低于$30kg/m^2$的病症;术语“II类肥胖症”是其中BMI等于或大于$30kg/m^2$的病症。

[0198] 术语“内脏型肥胖症”被定义为其中男性所测得的腰臀比大于或等于1.0,女性所测得的腰臀比大于或等于0.8的病症。其定义了胰岛素抵抗的风险和糖尿病前期的发展。术语“腹部肥胖症”通常被定义为其中男性腰围>40英寸或102cm,女性腰围>35英寸或94cm的病症(要了解人群的正常范围,参见例如“Joint scientific statement(IDF,NHLBI,AHA,WHO,IAS,IASO).Circulation 2009;120:1640-1645”)。

[0199] 本文中,术语“病态肥胖症”被定义为其中欧裔个体BMI>40或BMI>35且患有共病(诸如糖尿病或高血压)的病症(参见World Health Organization.Obesity:Preventing and Managing the Global Epidemic:Report on a WHO Consultation.World Health Organ Tech Rep Ser.2000;894:i-xii,1-253)。

[0200] 术语“血糖正常”被定义为如下病症:其中受检者具有在大于70mg/dL(3.89mmol/L)且小于100mg/dL(5.6mmol/L)正常范围内的空腹血液葡萄糖浓度,并且餐后2小时血糖浓度小于140mg/dl。

[0201] 术语“高血糖”被定义为如下病症:其中受检者具有高于正常范围,大于100mg/dL(5.6mmol/L)的空腹血液葡萄糖浓度。

[0202] 术语“低血糖”被定义为如下病症:其中受检者具有低于正常范围,尤其是低于70mg/dL(3.89mmol/L)的血液葡萄糖浓度。

[0203] 术语“餐后高血糖”被定义为如下病症:其中受检者具有大于200mg/dL(11.11mmol/L)的餐后2小时血液葡萄糖或血清葡萄糖浓度。

[0204] 术语“空腹血液葡萄糖受损”或“IFG”被定义为如下病症:其中受检者具有在100mg/dl至125mg/dl(即,5.6mmol/l至6.9mmol/l)范围内的空腹血液葡萄糖浓度或空腹血清葡萄糖浓度。具有“正常空腹血糖”的受检者具有小于100mg/dl,即小于5.6mmol/l的空腹血糖浓度。

[0205] 术语“葡萄糖耐量受损”或“IGT”被定义为如下病症:其中受检者具有大于140mg/dl(7.78mmol/L)且小于200mg/dL(11.11mmol/L)的餐后2小时血液葡萄糖或血清葡萄糖浓度。葡萄糖耐量异常即餐后2小时血液葡萄糖或血清葡萄糖浓度可以用禁食后服用75g葡萄糖之后2小时的血糖水平来测量,单位为mg葡萄糖/dL血浆。“葡萄糖耐量正常”的受检者具有小于140mg/dl(7.78mmol/L)的餐后2小时血液葡萄糖或血清葡萄糖浓度。

[0206] 术语“高胰岛素血症”被定义为如下病症:其中具有胰岛素抵抗的受检者(无论是否具有正常血糖)的空腹或餐后血清或血浆胰岛素水平升高到超过不具有胰岛素抵抗、腰臀比＜1.0(对于男性)或＜0.8(对于女性)的正常消瘦个体的水平。

[0207] 术语“胰岛素抵抗”被定义为如下状态:其中需要超过对葡萄糖负荷正常响应的循环胰岛素水平才能保持血糖正常状态(Ford E S等人,JAMA.(2002)287:356-9)。测定胰岛素抵抗的方法是正常血糖-高血胰岛素钳夹试验。胰岛素与葡萄糖之比在组合胰岛素-葡萄糖输注技术的范围内测定。如果葡萄糖吸收低于所研究的背景群体的25%,则认为存在胰岛素抵抗(WHO定义)。比钳夹试验繁复性更小的是所谓的极小模型,其中在静脉内葡萄糖耐量测试期间,以固定时间间隔测量血液中的胰岛素和葡萄糖浓度,然后以此计算胰岛素抵抗。使用该方法,无法区分肝胰岛素抵抗和外周胰岛素抵抗。

[0208] 通常,在日常临床实践中使用其他参数来评估胰岛素抵抗。优选地,例如因为甘油三酯水平升高与胰岛素抵抗的存在显著相关,所以使用患者的甘油三酯浓度来评估胰岛素抵抗。

[0209] 具有发展IGT或IFG或2型糖尿病的易感体质的患者是血糖正常且伴有高胰岛素血症的那些患者,并且按照定义,这些患者具有胰岛素抵抗。具有胰岛素抵抗的典型患者通常超重或肥胖。如果可检出胰岛素抵抗,则这是存在糖尿病前期的特别强的指征。因此,可能的情况是,为了维持葡萄糖动态平衡,人体需要健康人体2-3倍的胰岛素,若非如此,则会导致任何临床症状。

[0210] 术语“糖尿病前期”是其中个体存在发展成2型糖尿病的前期倾向的病症。糖尿病前期扩展了葡萄糖耐量受损的定义,将具有高正常范围100mg/dL内的空腹血液葡萄糖(J.B.Meigs等人,Diabetes 2003;52:1475-1484)和空腹高胰岛素血症(血浆胰岛素浓度升高)的个体纳入在内。用于将糖尿病前期鉴定为严重健康威胁的科学和医学依据在名称为“The Prevention or Delay of Type 2Diabetes”的立场声明中提出,该立场声明由美国糖尿病协会(American Diabetes Association)和国立糖尿病消化与肾病研究所(National Institute of Diabetes and Digestive and Kidney Diseases)联合发表(Diabetes Care 2002;25:742-749)。容易具有胰岛素抵抗的个体为具有以下属性中两个或更多个的那些个体:1)超重或肥胖,2)高血压,3)高血脂,4)存在一名或多名一级亲属被诊断出IGT或IFG或2型糖尿病。

[0211] 术语“2型糖尿病”被定义为如下病症:其中在最少两个独立场合测量时,受检者具有大于125mg/dL(6.94mmol/L)的空腹(即,8小时内无卡路里摄入)血液葡萄糖或血清葡萄

糖浓度。血液葡萄糖值的测量采用常规医疗分析中的标准程序。2型糖尿病也被定义为如下病症:其中受检者具有等于或大于6.5%的HbA1c、在口服葡萄糖耐量测试(OGTT)期间等于或大于200mg/dL(11.1mmol/L)的两小时血浆葡萄糖、或等于或大于200mg/dL(11.1mmol/L)的随机葡萄糖浓度,并伴有高血糖或高血糖危象的经典症状。在没有明确高血糖症状时,与大多数诊断性测试一样,应重复诊断出糖尿病的测试结果以排除实验室误差。应使用经国家糖化血红蛋白标准化计划(NGSP)认证,并经糖尿病控制和并发症研究(DCCT)参考测定法标准化或可溯源的方法进行HbA1c的评估。如果执行OGTT,则在空腹状态下服用75g葡萄糖之后2小时,糖尿病的血糖水平将超过200mg葡萄糖/dL血浆(11.1mmol/l)。在葡萄糖耐量测试中,在空腹最少8小时之后、通常在空腹10-12小时之后给待测试的患者口服施用75g葡萄糖,并在即将服用葡萄糖之前及服用葡萄糖1和2小时之后记录血糖水平。对于健康受检者,其在服用葡萄糖之前的血糖水平将介于60mg/dL与110mg/dL血浆之间,在服用葡萄糖1小时之后血糖水平将小于200mg/dL,并且在2小时之后血糖水平将小于140mg/dL。如果2小时之后,该值介于140mg与200mg之间,这认为存在葡萄糖耐量异常。

[0212] 术语"晚期2型糖尿病"包括具有长期糖尿病、继发性药物失效、胰岛素治疗指征,以及可能向微血管并发症和大血管并发症例如糖尿病性肾病或冠心病(CHD)进程的患者。

[0213] 术语"1型糖尿病"被定义为如下病症:其中在存在对胰β-细胞的自身免疫性的情况下(即,检测循环胰岛细胞自身抗体["1A型糖尿病"],即下列中的至少一种:GAD65[谷氨酸脱羧酶-65]、ICA[胰岛细胞细胞质]、IA-2[类酪氨酸磷酸酶蛋白质IA-2的细胞质内区域]、ZnT8[锌运输蛋白-8]或抗胰岛素;或在不存在典型的循环自身抗体的情况下,其它自身免疫性病症[1B型糖尿病],即,如通过胰腺活组织检查或成像所检测的),受检者具有大于125mg/dL(6.94mmol/L)的空腹(即,8小时内无卡路里摄入)血液葡萄糖或血清葡糖糖浓度。1型糖尿病也被定义为如下病症:其中在存在对于胰β-细胞的自身免疫性的情况下,受检者具有等于或大于6.5%的HbA1c、在口服葡萄糖耐量测试(OGTT)期间等于或大于200mg/dL(11.1mmol/L)的两小时血浆葡萄糖、或等于或大于200mg/dL(11.1mmol/L)的随机葡萄糖,并伴有高血糖或高血糖危象的经典症状。在没有明确高血糖症状时,与大多数诊断性测试一样,应重复诊断出糖尿病的测试结果以排除实验室误差。血液葡萄糖值的测量采用常规医疗分析中的标准程序。应使用经国家糖化血红蛋白标准化计划(NGSP)认证,并经糖尿病控制和并发症研究(DCCT)参考测定法标准化或可溯源的方法进行HbA1c的评估。如果执行OGTT,则在存在对于胰β细胞的自身免疫的情况下,在空腹状态下服用75g葡萄糖之后2小时,糖尿病的血糖水平将超过200mg葡萄糖/dL血浆(11.1mmol/l)。在葡萄糖耐量测试中,在空腹最少8小时之后、通常在空腹10-12小时之后给待测试的患者口服施用75g葡萄糖,并在即将服用葡萄糖之前及服用葡萄糖1和2小时之后记录血糖水平。某些基因(例如,HLA、INS VNTR和PTPN22)通常使人体存在遗传易感性,但并非总是如此。

[0214] 术语"MODY"("青春晚期糖尿病")描述了糖尿病的单基因形式,其根据基因影响,被分成MODY变体,例如MODY 1,2.3.4等。

[0215] 术语"LADA"("成人隐匿性自身免疫性糖尿病")是指患者被临床诊断为具有2型糖尿病,但检出具有对于胰β细胞的自身免疫。

[0216] 术语"HbA1c"是指血红蛋白β链的非酶糖基化产物。其测定法为本领域技术人员所熟知。在糖尿病治疗的监测过程中,HbA1c值非常重要。由于HbA1c的产生主要依赖于血糖水

平及红细胞寿命，因此“血糖记忆”意义上的HbA1c反映了先前4-6周的平均血糖水平。通过糖尿病强化治疗始终很好地调节HbA1c值(即样品中＜6.5％的总血红蛋白)，会给糖尿病患者带来明显更好的对于糖尿病性微血管病的防护。例如，单独使用二甲双胍时可使糖尿病患者的HbA1c值平均改善约1.0％-1.5％。在所有糖尿病患者中HbA1C值的这种减少不足以达到所期望的＜6.5％、且优选＜6％HbA1c的目标范围。

[0217] 本发明范围内的术语“血糖控制不足”或“血糖控制不充分”是指患者显示出的HbA1c值高于6.5％、尤其是高于7.0％、甚至更优选地高于7.5％、尤其是高于8％的病症。

[0218] “代谢综合征”也称为“X综合征”(当用于代谢紊乱语境中时)，还称为“异常代谢综合征”，是一种以胰岛素抵抗为主要特征的复杂综合征(Laaksonen D E等人，AmJ Epidemiol 2002;156:1070-7)。根据ATP III/NCEP指南(Executive Summary of the Third Report of the National Cholesterol Education Program(NCEP)Expert Panel on Detection,Evaluation,and Treatment of High Blood Cholesterol in Adults (Adult Treatmem Panel III)JAMA:Journal of the American Medical Association (2001)285:2486-2497)，当存在三种或更多种以下风险因子时，进行代谢综合征的诊断：

[0219] 1.腹部肥胖症，其定义为男性腰围大于约40英寸或102cm，女性腰围大于约35英寸或94cm；

[0220] 2.甘油三酯等于或大于约150mg/dL；

[0221] 3.男性HDL-胆固醇小于约40mg/dL，女性HDL-胆固醇小于约50；

[0222] 4.血压等于或大于约130/85mmHg(SBP等于或大于约130，或DBP等于或大于约85)；

[0223] 5.空腹血液葡萄糖等于或大于约100mg/dL。

[0224] 根据常用定义，如果收缩压(SBP)的值超过1401mnHg且舒张压(DBP)的值超过90mmHg，则诊断为高血压。如果患者罹患显性糖尿病，则目前推荐将收缩压降至低于130mmHg，且将舒张压降至低于80mmHg的程度。

[0225] NODAT(移植后新发糖尿病)及PTMS(移植后代谢综合征)的定义密切遵循美国糖尿病协会(American Diabetes Association)关于2型糖尿病诊断标准的定义，以及国际糖尿病联合会(International Diabetes Federaion，IDF)与美国心脏协会/美国国家心脏、肺及血液研究所(American Heart Association/National Heart,Lung,and Blood Institute)关于代谢综合征的定义。NODAT和/或PTMS与微血管及大血管疾病和事件、移植排斥、感染及死亡的风险增加有关。已将多种预测因子确定为与NODAT和/或PTMS相关的潜在风险因素，包括移植时较高的年龄、男性性别、移植前身体质量指数、移植前糖尿病及免疫抑制。

[0226] 术语“妊娠期糖尿病”(孕期糖尿病)表示发展于怀孕期间且通常在产后又立即结束的糖尿病形式。妊娠期糖尿病通过筛查测试来诊断，该筛查测试常在怀孕第24周至第28周进行，但也可在怀孕期的任何时间进行，特别是已诊断出既往曾患妊娠期糖尿病的情况下。该测试一般较为简单，其中在施用50g葡萄糖溶液之后一小时，测量血糖水平。若此1小时水平高于140mg/dl，则疑似患有妊娠期糖尿病。最终确认可通过标准葡萄糖耐受测试来获得，例如利用75g的葡萄糖；在不存在50g测试用的情况下，其还用作诊断测试。

[0227] 如本文所用，除非另有说明，否则术语“肥胖症相关疾病”应当是指特征在于过量的体重的任何疾病、障碍或病症，或者由于过重而恶化、加剧或其进程被加速的任何疾病、

障碍或病症。还包括其中所述疾病、障碍或病症的至少一个症状或表现由于过重而恶化、加剧或其进程被加速的任何疾病、障碍或病症。肥胖症相关疾病的适宜示例包括但不限于：

[0228] (a)超重或肥胖症；

[0229] (b)代谢紊乱，诸如糖尿病前期、口服葡萄糖耐量受损、空腹血液葡萄糖受损、胰岛素抵抗、1型糖尿病、2型糖尿病、青春晚期糖尿病(MODY)、成人隐匿性自身免疫性糖尿病(LADA)、NODAT、妊娠期糖尿病、高血糖、餐后高血糖、高胰岛素血症、血糖控制不足(或血糖控制不充分)和X综合征(也被称为代谢综合征)等；

[0230] (c)肾或脂肪肝疾病(诸如酒精性单纯性脂肪肝、酒精性脂肪性肝炎(ASH)、酒精性肝纤维化、酒精性肝硬化、非酒精性脂肪肝病(NAFLD)、非酒精性单纯性脂肪肝、非酒精性脂肪性肝炎(NASH)、非酒精性肝纤维化和非酒精性肝硬化、过度滤过性糖尿病性肾病、肾过度滤过、肾小球过度滤过、肾同种异体移植过度滤过、代偿性过度滤过、过度滤过性慢性肾病、过度滤过性急性肾衰竭、微量白蛋白尿(高尿白蛋白水平)、大量白蛋白尿、高尿白蛋白水平、高白蛋白/肌酸酐比率(ACR)、慢性肾脏疾病(CKD)、急性肾衰竭(ARF)等；

[0231] (d)MACE或心血管事件(诸如，心肌梗塞、不稳定型心绞痛、心血管死亡、脉管再通、致命或非致命脑血管意外、外周动脉病、主动脉事件和由于充血性心力衰竭的住院等)；

[0232] 以及(e)睡眠障碍(诸如睡眠呼吸暂停等)。

[0233] 如本文所用，术语“受检者”是指已成为治疗、观察或实验对象的动物，优选指哺乳动物，最优选指人。

[0234] 在本发明的某些实施方案中，受检者超重或肥胖。在本发明的附加实施方案中，受检者超重或肥胖并且经诊断患有或表现出肥胖症相关疾病的至少一种症状。在本发明的附加实施方案中，受检者具有大于或等于约25kg/m^2，优选地大于或等于约30kg/m^2的经测量或测定的BMI。

[0235] 在本发明的某些实施方案中，受检者是糖尿病者。在本发明的某些实施方案中，受检者是糖尿病前期的。在本发明的某些实施方案中，受检者是非糖尿病者。

[0236] 如本文所用，除非另有说明，否则术语“治疗(动词)”、“治疗(名词)”等应包括为对抗疾病、病症或障碍而对受检者或患者(优选为哺乳动物，更优选为人)进行的管理和护理。术语“治疗(动词)”或“治疗(名词)”包括施用如本文所述的化合物或药物组合物，以(a)减轻疾病、病症或障碍的一种或多种症状或并发症；(b)预防疾病、病症或障碍的一种或多种症状或并发症发病；和/或(c)消除疾病、病症或障碍的一种或多种症状或并发症。

[0237] 如本文所用，除非另有说明，否则术语“延迟.....的进程”和“减慢.....的进程”应当包括：(a)延迟或减慢疾病、病症或障碍的一种或多种症状或并发症的发展；(b)延迟或减慢疾病、病症或障碍的一种或多种新型/附加症状或并发症的发展；和/或(c)延缓或减慢疾病、病症或障碍的进展成所述疾病、病症或障碍的后续阶段或更严重形式。

[0238] 如本文所用，除非另有说明，否则术语“进行预防”和“预防”应包括(a)降低一种或多种症状的频率；(b)减轻一种或多种症状的严重程度；(c)延迟、减慢或避免一种或多种附加症状的发展；和/或(d)延迟、减慢或避免障碍、病症或疾病发展成后续阶段或更严重的形式。

[0239] 本领域技术人员将认识到，在本发明涉及预防方法的情况下，有需要的受检者(即需要进行预防的受治疗者)应包括任何已经历或表现出待预防的障碍、疾病或病症中的至

少一种症状的受检者或患者(优选地为哺乳动物,更优选地为人)。此外,有需要的受检者还可以是没有表现出待预防的障碍、疾病或病症中的任何症状,但被医师、临床医生或其他医疗专业人员认为具有发展所述障碍、疾病或病症的风险的受检者(优选地为哺乳动物,更优选地为人)。例如,由于该受检者的病史,包括但不限于家族史、易患病的体质、共存的(共病)障碍或病症、遗传测试等,该受检者可被认为具有发展障碍、疾病或病症的风险(并因此需要预防或预防性治疗)。

[0240] 本文所用的术语"治疗有效量"意指能在组织系统、动物或人体上引起研究人员、兽医、医生或其他临床医师正在寻求的生物或药物反应(包括所治疗疾病或障碍的症状的缓解)的活性化合物或药剂的量。

[0241] 其中本发明涉及协同治疗或联合治疗,其包括施用以下物质:(a)卡格列净和(b)芬特明,"治疗有效量"应当是指使得组合效应引起所需生物或药物响应的一起摄入的药剂组合的量。例如,包括施用(a)卡格列净和(b)芬特明的协同治疗的治疗有效量,将是一起或依次服用时具有治疗有效的组合效果的(a)卡格列净的量和(b)芬特明的量。此外,本领域技术人员应认识到在如上示例中所述,具有治疗有效量的协同治疗或联合治疗的情况下,(a)卡格列净的量和/或(b)芬特明的量在单独给药时可能有疗效或可能无疗效。

[0242] 如本文所用,术语"协同治疗"和"联合治疗"应当是指通过施用(a)卡格列净和(b)芬特明治疗对其有需要的受检者,其中(a)卡格列净和(b)芬特明通过适宜的方式,同时、顺序、单独或以单一药物制剂的形式施用(只要卡格列净和芬特明在某种程度上同时存在于受检者中即可)。在(a)卡格列净和(b)芬特明以分开的剂型施用的情况下,每种化合物每天施用的剂量数可以相同或不同。(a)卡格列净和(b)芬特明可通过相同或不同的给药途径给药。合适的给药方法的示例包括但不限于口服给药、静脉内给药(iv)、肌内给药(im)、皮下给药(sc)、经皮给药和直肠给药。(a)卡格列净和(b)芬特明还可直接施用于神经系统,包括但不限于脑内施用、心室内施用、脑室内施用、鞘内施用、脑池内施用、脊柱内施用和/或脊髓周围施用途径,这些施用途径通过颅内或脊椎内针和/或导管在具有或不具有泵装置的情况下递送。可根据同时或交替方案、在治疗过程中的同一时间或不同时间、同时以分开形式或单一形式施用(a)卡格列净和(b)芬特明。

[0243] 本发明涉及如本文所述的联合治疗或协同治疗。联合治疗或协同治疗是有利的,因为在某些情况下,活性成分的协同施用实现的治疗效果大于通过仅施用单一治疗剂实现的治疗效果。

[0244] 在某些实施方案中,两种或更多种治疗剂的协同施用(联合治疗或协同治疗)实现的治疗效果大于通过仅施用单一治疗剂实现的治疗效果。就这一点而言,一种治疗剂的治疗效果通过协同施用另一治疗剂来增强。在某些实施方案中,两种或更多种治疗剂的协同施用实现等于约由施用每种单一治疗剂所实现的治疗效果的总和的治疗效果。在这些实施方案中,联合治疗被认为是"累加的"。在某些实施方案中,两种或更多种治疗剂的协同施用实现协同效果,即大于组合的单独组分的治疗效果的总和的治疗效果。

[0245] 在某些实施方案中,治疗剂以单一剂型施用,其中每种单独的治疗剂与其它治疗剂分离。以此类方式配制剂型有助于维持潜在反应性治疗剂的结构完整性直至其被施用。该类型的制剂在制备期间以及对于剂型的长期储存可能是有用的。在某些实施方案中,治疗剂可包含隔离区域或不同囊片等容纳于胶囊中。在某些实施方案中,治疗剂以片剂所包

含的独立的层形式提供。

[0246] 另选地，治疗剂可以独立组合物，例如独立的片剂或溶液形式施用。一种或多种活性剂可与其它活性剂同时施用，或者活性剂可间歇式施用。可调节治疗剂的施用之间的时间长度以实现期望的治疗效果。在某些情况下，一种或多种治疗剂可在施用其它治疗剂之后仅数分钟(例如，约1、2、5、10、30或60分钟)来施用。另选地，一种或多种治疗剂可在施用其它治疗剂之后数小时(例如，约2、4、6、10、12、24或36小时)来施用。在某些实施方案中，可能有利的是在施用剩余治疗剂之间施用一种或多种治疗剂的多于一种剂量。例如，一种治疗剂可在施用其它治疗剂之后的2小时施用，并且然后在10小时后再次施用。重要的是，需要各种活性成分的治疗效果重叠每种治疗剂的持续时间的至少一部分使得联合治疗的总体治疗效果可部分地归因于联合治疗的组合效应或协同效应。

[0247] 因为两种或更多种不同活性剂一起用于联合治疗中，所以必须考虑每种试剂的效能和它们一起使用所实现的交互效应。重要的是，对于特定哺乳动物的剂量范围和最佳剂量的测定也完全在受益于本公开的本领域普通技术人员的能力内。

[0248] 术语“协同”是指比任两种或更多种单一试剂的累加效应更有效的组合。协同效应允许使用较低量(剂量)的单独治疗来有效治疗疾病、障碍或病症。较低剂量导致较低毒性但不降低功效。此外，协同效应可导致改善的功效。最终，与任何单一治疗相比，协同作用可导致改善的疾病的避免或减少。

[0249] 与在单独使用任一药物时通常所需的相比，联合治疗可允许较低剂量的第一治疗剂或第二治疗剂(本文被称为“明显的单向协同作用”)或较低剂量的两种治疗剂(本文中被称为“双向协同作用”)的产品。在某些实施方案中，一种或多种治疗剂和剩余治疗剂之间表现出的协同作用为如果在不具有其它治疗剂的剂量的情况下施用，则治疗剂中的一种的剂量将是亚治疗这样的协同作用。

[0250] 术语“增强”或“加强”是指其中化合物中一种增加或增强施用于患者的另一种或多种化合物的治疗效应的组合。在一些情况下，增强可导致改善具体治疗的功效、耐药性、或安全性、或它们的任何组合。

[0251] 在某些实施方案中，本发明涉及一种药物组合物，该药物组合物包含治疗有效剂量的一种或多种治疗剂连同有效增强一种或多种治疗剂的治疗效果的一定剂量的另一种治疗剂。在其它实施方案中，本发明涉及通过向患者施用另一治疗剂增强一种或多种治疗剂在患者中的治疗效果的方法。

[0252] 在某些实施方案中，本发明部分地涉及以足以获得治疗效果的量将一种或多种治疗剂连同剩余治疗剂协同组合。例如，在某些实施方案中，获得的治疗效果是由单独的一种或多种治疗剂的剂量所获得的治疗效果至少约2(或至少约4、6、8或10)倍。在某些实施方案中，协同组合提供的治疗效果是由单独的一种或多种治疗剂的剂量所获得的治疗效果至多约20、30或40倍。在此类实施方案中，协同组合显示在本文中被称为“明显的单向协同作用”的现象，这是指剩余治疗剂的剂量协同地增强一种或多种治疗剂的效果，但一种或多种治疗剂的剂量看起来不显著增强剩余治疗剂的效果。

[0253] 在某些实施方案中，活性剂的组合表现出双向协同作用，这是指第二治疗剂增强第一治疗剂的效果，并且第一治疗剂增强第二治疗剂的效果。因此，本发明的其它实施方案涉及第二治疗剂和第一治疗剂的组合，其中每种药物的剂量由于药物之间的协同作用而减

少，并且来源于剂量减少的药物的组合的治疗效果增强。由于第一治疗剂对第二治疗剂的效能比率，双向协同作用在实际剂量中通常不容易显而易见。例如，当一种治疗剂相对于其它治疗剂显示出大得多的治疗效能时，双向协同作用可能难以检测。

[0254] 联合治疗的协同效应可通过生物活性测定来评价。例如，治疗剂在被设计用于基于EC_{90}或EC_{50}值给出大致等效的治疗效果的摩尔比下混合。因此，将三种不同的摩尔比用于每种组合以允许在评估相对效能时的可变性。这些摩尔比可在整个稀释系列中维持。对应的单一治疗也使用标准主要测定形式平行于联合治疗来评价。联合治疗的治疗效果与单一治疗的治疗效果的比较给出了协同效应的量度。组合分析的设计方面的进一步细节可见于B E Korba(1996)Antiviral Res.29:49。协同、累加和拮抗的分析可使用CalcuSyn™程序(Biosoft，Inc.)通过前述数据的分析来确定。该程序通过使用普遍被接受的Chou和Talalay的方法与使用Monte Carlo统计包的统计学评价的组合来评价药物相互作用。数据以若干不同格式来显示，包括中值效应和剂量效应曲线、等效线图、和带标准偏差的组合指数[CI]曲线。就后一分析而言，CI大于1.0指示拮抗，而CI小于1.0指示协同。

[0255] 本发明的组合物呈现出获得缓解中度到严重疾病的情况的机会。由于由本发明的第一和第二治疗剂的组合提供的协同或累加或增强效应，可能的是使用剂量减少的每一种治疗剂。通过使用较少量的药物，与各药物相关的副作用可以在数量和程度上减少。此外，本发明组合避免了一些患者对其特别敏感的副作用。本发明提供了药学上可接受的组合物，其包含治疗有效量的两种或更多种本文所述的化合物，所述化合物与一种或多种药学上可接受的载体(添加剂)和/或稀释剂一起配制。如本文详细描述的，本发明的药物组合物可具体地被配制成以固体或液体形式施用，包括适用于下列的那些：(1)口服给药，例如，药水(水溶液或非水溶液或悬浮液)，片剂，例如用于颊部、舌下和全身吸收的那些片剂，大丸剂、散剂、颗粒剂、施用于舌部的糊剂；(2)肠胃外给药，例如通过皮下、肌内注射、静脉内或硬膜外注射，例如无菌溶液或悬浮液或缓释制剂；(3)局部施用，例如，以施用于皮肤的霜膏、膏剂、或缓释贴剂或喷雾的形式；(4)阴道内或直肠内，例如，以栓剂、霜膏或泡沫形式；(5)舌下；(6)经眼；(7)经皮；或(8)经鼻。

[0256] 对于在医学中使用而言，本发明的化合物的盐类是指无毒的“药学上可接受的盐”。然而，其它盐类也可用于制备根据本发明的化合物或其药学上可接受的盐。化合物的合适的药学上可接受的盐包括酸加成盐，其可(例如)通过将该化合物的溶液与药学上可接受的酸(诸如盐酸、硫酸、富马酸、马来酸、琥珀酸、乙酸、苯甲酸、柠檬酸、酒石酸、碳酸或磷酸)的溶液混合来形成。此外，如果本发明的化合物具有酸性部分，其合适的药学上可接受的盐可包括碱金属盐，例如钠盐或钾盐；碱土金属盐(例如钙盐或镁盐)；和与合适的有机配体形成的盐(例如季铵盐)。因此，代表性的药学上可接受的盐包括如下：乙酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、硫酸氢盐、酒石酸氢盐、硼酸盐、溴化物、依地酸钙盐、樟脑磺酸盐、碳酸盐、氯化物、克拉维酸盐、柠檬酸盐、二氢氯化物、依地酸盐、乙二磺酸盐、依托酸盐、乙磺酸盐、富马酸盐、葡庚糖酸盐、葡萄糖酸盐、谷氨酸盐、对羟乙酰氨基苯肿酸盐、己基苯间二酚盐、海巴明盐、氢溴酸盐、盐酸盐、羟基萘甲酸盐、碘化物、异硫代硫酸盐、乳酸盐、乳糖酸盐、月桂酸盐、苹果酸盐、马来酸盐、扁桃酸盐、甲磺酸盐、甲基溴化物、甲基硝酸盐、甲基硫酸盐、粘酸盐、萘磺酸盐、硝酸盐、N-甲基葡糖胺铵盐、油酸盐、双羟萘酸盐(恩波酸盐)、棕榈酸盐、泛酸盐、磷酸盐/二磷酸盐、聚半乳糖醛酸盐、水杨酸盐、硬脂酸盐、硫酸盐、碱式乙酸

盐、琥珀酸盐、单宁酸盐、酒石酸盐、茶氯酸盐、甲苯磺酸盐、三乙基碘化物和戊酸盐。

[0257] 可用于制备药学上可接受的盐的代表性酸和碱包括下列：酸，包括乙酸、2,2-二氯乙酸、乙酰化的氨基酸、己二酸、藻酸、抗坏血酸、L-天冬氨酸、苯磺酸、苯甲酸、4-乙酰氨基苯甲酸、(+)-樟脑酸、樟脑磺酸、(+)-(1S)-樟脑-10-磺酸、癸酸、己酸、辛酸、肉桂酸、柠檬酸、环拉酸、十二烷基硫酸、乙烷-1,2-二磺酸、乙磺酸、2-羟基-乙磺酸、甲酸、富马酸、半乳糖二酸、龙胆酸、葡庚糖酸、D-葡糖酸、D-葡萄糖醛酸、L-谷氨酸、α-氧代-戊二酸、乙醇酸、马尿酸、氢溴酸、盐酸、(+)-L-乳酸、(±)-DL-乳酸、乳糖酸、马来酸、(-)-L-苹果酸、丙二酸、(±)-DL-扁桃酸、甲磺酸、萘-2-磺酸、萘-1,5-二磺酸、1-羟基-2-萘甲酸、烟酸、硝酸、油酸、乳清酸、草酸、棕榈酸、扑酸、磷酸、L-焦谷氨酸、水杨酸、4-氨基-水杨酸、癸二酸、硬脂酸、琥珀酸、硫酸、鞣酸、(+)-L-酒石酸、硫氰酸、对甲苯磺酸和十一碳烯酸；和碱，包括氨、L-精氨酸、苯乙苄胺、苄星、氢氧化钙、胆碱、丹醇、二乙醇胺、二乙胺、2-(二乙基氨基)-乙醇、乙醇胺、乙二胺、N-甲基-葡萄糖胺、海巴明、1H-咪唑、L-赖氨酸、氢氧化镁、4-(2-羟乙基)-吗啉、哌嗪、氢氧化钾、1-(2-羟乙基)-吡咯烷、仲胺、氢氧化钠、三乙醇胺、氨基丁三醇和氢氧化锌。

[0258] 为了提供更简明的描述，本文给出的一些数量表述没有用术语“约”修饰。应当理解，无论是否明确地使用了术语“约”，本文所给出的每个量都意在指代实际的给定值，并且还意在指代由本领域的普通技术人员可合理推测出的这些给定值的近似值，包括这些给定值的由实验和/或测量条件所引起的近似值。此外，为了提供更简洁的描述，本文中一些定量表述被叙述为约X量至约Y量的范围。应当理解，当叙述范围时，所述范围并不限制于所叙述的上下界限，而应包括约X量至约Y量的整个范围或者它们之间的任何量或范围。

[0259] 药物组合物

[0260] 如本文所用，术语“组合物”旨在涵盖包含指定量的指定成分的产品，以及通过组合指定量的指定成分而直接或间接得到的任何产品。

[0261] 本发明还包括药物组合物，该药物组合物包含(a)卡格列净、和(b)芬特明以及药学上可接受的载体。可以根据常规的药物配混技术，通过将一种或多种化合物与药用载体紧密混合来制备包含(a)卡格列净和(b)芬特明作为活性成分的药物组合物。取决于期望的给药途径(如口服给药、肠胃外给药)，载体可采取多种形式。因此对于诸如混悬剂、酏剂和溶液剂的液体口服制剂，合适的载体和添加剂包括水、二元醇、油、醇类、矫味剂、防腐剂、稳定剂、着色剂等；对于诸如散剂、胶囊剂和片剂之类的固体口服制剂，合适的载体和添加剂包括淀粉、糖、稀释剂、粒化剂、润滑剂、粘结剂、崩解剂等。固体口服制剂还可包覆有物质诸如糖或包覆有肠溶衣，以便调节主要的吸收位点。对于肠胃外给药，载体将通常由无菌水组成，并可加入其他成分以增加溶解度或防腐性。注射用混悬剂或溶液剂也可以利用水基载体连同合适的添加剂来制备。

[0262] 为了制备本发明的药物组合物，根据常规的药物配混技术，将作为活性成分的(a)卡格列净和(b)芬特明与药用载体紧密混合，该载体取决于给药(如口服给药或诸如肌内注射的肠胃外给药)所期望的制剂形式而可采取多种形式。在制备口服剂型的组合物时，可以采用任何可用的药用介质。因此对于诸如混悬剂、酏剂和溶液剂之类的液体口服制剂，合适的载体和添加剂包括水、二元醇、油、醇类、矫味剂、防腐剂、着色剂等；对于固体口服制剂(诸如例如散剂、胶囊剂、囊片、胶囊锭剂和片剂)，合适的载体和添加剂包括淀粉、糖、稀释

剂、粒化剂、润滑剂、粘结剂、崩解剂等。由于其在给药方面的方便性，片剂和胶囊剂代表了最有利的口服单位剂型，在这种情况下显然采用固体药学上可接受的载体。如果需要，片剂可通过标准技术包糖衣或包肠溶衣。对于胃肠外给药，载体将通常包含无菌水，但还可包含其他成分，例如用于诸如帮助溶解或防腐之类的目的。还可以制备注射用混悬剂，在这种情况下，可以采用合适的液体载体、悬浮剂等。本发明的药物组合物每剂量单位(例如，每片、每粒胶囊、每份散剂、每支注射剂、每茶匙等)将包含递送上述有效剂量必需的活性成分的量。本文的药物组合物每单位剂量单位(例如每片、每粒胶囊、每份散剂、每支注射剂、每支栓剂、每茶匙等)将含有约0.1mg至约1000mg或其中的任何量或范围，并且可以约0.01-200.0mg/kg/天，优选地约0.05至100mg/kg/天，更优选地约0.05-50mg/kg/天，更优选地约0.05-25.0mg/kg/天，更优选地约0.05-10.0mg/kg/天，最优选地约0.5至约7.5mg/kg/天或其中的任何范围的剂量给药。然而，根据患者的需要、所治疗的病症的严重程度和所采用的化合物，剂量可以有所不同。可采用每日给药或周期后给药的使用方式。

[0263] 优选地，这些组合物为单位剂型，例如片剂、丸剂、胶囊剂、散剂、颗粒剂、无菌肠胃外溶液剂或混悬剂、计量气雾剂或液体喷雾剂、滴剂、安瓿剂、自动注射装置或栓剂；用于口服、肠胃外给药、鼻内给药、舌下给药或直肠给药，或用于经吸入或吹入给药。另选地，组合物可以适于每周一次或每月一次给药的方式提供。例如，活性化合物的不溶性盐(如癸酸盐)可适于提供用于肌内注射的长效制剂。为制备固体组合物诸如片剂，将主要的活性成分与药学上可接受的载体(例如常规的制片成分，诸如玉米淀粉、乳糖、蔗糖、山梨醇、滑石粉、硬脂酸、硬脂酸镁、磷酸二钙或树胶)以及其它药用稀释剂(例如水)混合，以形成含有本发明的化合物或其药学上可接受的盐的均匀混合物的固体预配制组合物。当将这些预配制组合物称为均匀时，意指活性成分在整个组合物中均匀分散，使得该组合物可容易细分成等效剂型，诸如片剂、丸剂和胶囊剂。然后将这个固体预配制组合物分成含有0.1至约1000mg或者其中任何数量或范围的本发明活性成分的上述类型的单位剂量形式。可将该新组合物的片剂或丸剂进行包覆或以其他方式配混，以得到能提供长效优点的剂型。例如，片剂或丸剂可包含内剂型组分和外剂型组分，后者为在前者上面的包层的形式。这两种组分可通过肠溶层分开，该肠溶层起到防止在胃中崩解的作用，并且使内组分完整地进入十二指肠或得以延迟释放。多种材料可被用于此类肠溶层或包衣，此类材料包括与诸如紫胶、鲸蜡醇和乙酸纤维素之类的材料一起的多种聚合酸材料。

[0264] 可掺入本发明新型组合物用于口服或注射施用的液体制剂包括水溶液剂、适当矫味的糖浆剂、水性或油性混悬剂和用食用油(棉籽油、芝蔴油、椰子油或花生油)矫味的乳剂，以及酏剂和类似药用介质。适用于水性混悬剂的分散剂或悬浮剂包括合成树胶或天然树胶，诸如黄蓍胶、阿拉伯树胶、藻酸盐、葡聚糖、羧甲基纤维素钠、甲基纤维素、聚乙烯吡咯烷酮或明胶。

[0265] 为了制备本发明的某些药物组合物，根据常规的药物配混技术，可将作为活性成分的卡格列净和作为活性成分的芬特明各自与药用载体紧密混合，取决于给药(如口服或肠胃外给药)所需的制剂形式，该载体可采取多种形式并且此后分别组合在一起。为了制备本发明的其它药物组合物，根据常规的药物配混技术，可将作为活性成分的卡格列净和芬特明与药用载体紧密混合，取决于给药(如口服或肠胃外给药)所需的制剂形式，该载体可采取多种形式。合适的药学上可接受的载体是本领域所熟知的。这些药学上可接受的载体

中的一些的描述可见于美国药学协会(American Pharmaceutical Association)和英国药学会(Pharmaceutical Society of Great Britain)出版的The Handbook of Pharmaceutical Excipients(《药用辅料手册》)中,该文献的公开内容据此以引用方式并入。

[0266] 配制药物组合物的方法描述于多个出版物,诸如Pharmaceutical Dosage Forms:Tablets,Second Edition,Revised and Expanded,第1-3卷,由Lieberman等人编辑;Pharmaceutical Dosage Forms:Parenteral Medications,第1-2卷,由Avis等人编辑;和Pharmaceutical Dosage Forms:Disperse Systems,第1—2卷,由Lieberman等人编辑;由Marcel Dekker,Inc.出版,这些文献的公开内容据此以引用方式并入。

[0267] 除了用于治疗肥胖症的药物溶液之外,各种医疗装置已经被开发出来用于治疗肥胖症,并且被引入临床实践中。虽然这些装置中许多仍然处于临床试验中,但研究者对于其作为用于肥胖症的低苛刻性、高效治疗的组件的前景仍然保持乐观。此外,这些装置的重要性由于许多严重肥胖患者不是手术介入的理想候选者而被突显。因此,此类装置允许为遭受肥胖症和其它代谢病症的患者提供新的治疗选项,并且在一些情况下可为更加侵入式的手术方法提供有价值的替代方案。

[0268] 腔内套管是被开发用于治疗肥胖症的一个示例。这些套管在摄取的食物和肠壁之间形成物理屏障,从而通过控制食物如何移动通过消化系统来改变代谢途径。这种小肠的机械旁路模拟了对胃旁路术患者代谢的影响,通常导致严重的体重减轻和2型糖尿病的缓解。所述装置可以内窥镜形式(经由嘴部)植入并移除,而不需要手术介入。

[0269] 胃内球囊是第二示例。胃内球囊被设计用于占据胃内容量,使得更少量的食物产生饱腹感。目前市面上的胃内球囊不固定于胃中,并且因此可导致并发症诸如栓塞和粘膜糜烂。为避免这些并发症,球囊在最多六个月之后移除。一项研究发现一年之后的平均过量体重减轻为约48.3%。然而,患者报道发生恶心和呕吐;并且少量患者患有上腹部疼痛。此外,约0.6%的患者发生球囊嵌塞。固定至胃壁的球囊可潜在地改善该方法的总体安全性和功效,并且允许长期植入。

[0270] 还已经开发了减少或再分配患者的胃肠内腔的容积的装置。此类装置的示例包括锚定件,其一旦被采用,就减小患者的GI道内的横截面积。具体地讲,多种该类型的相关装置(诸如钉、盲钉、束带、夹子、销钉、粘合剂和螺钉)已用于减少或再分配胃肠内腔的容积。

[0271] 另一方法涉及使用电流来刺激胃或消化道的某些神经。Medtronic(Minneapolis)已经开发出一种电池供电的、秒表大小的胃调节器(类似于心脏起搏器),其导致胃收缩,发送安全信号到脑中的食欲中枢。该胃调节器植入到腹腔的皮肤下,其中电线置于胃壁上。另外,电将通过调节食欲信号来改变饮食行为。另外,胃调节器还可用于促进代谢,这可导致进一步体重减轻。

[0272] 还已经开发出使用电荷以抑制通向胃的主要神经(迷走神经)的植入物。在这种情况下,电荷可减慢消化;例如,由于刺激,胃将不指示食物的存在,并且因此将不引发消化过程。通过下调迷走神经的活性,该技术同时控制与肥胖症有关的多个主要生物功能,包括食物摄取、饥饿感知和消化。此外,该调节是可逆的,并且该治疗可被调节并程序化以满足个体患者的治疗需要。

[0273] 脑部深层刺激技术也被开发作为肥胖症的一种可能的治疗,其使用植入于脑部的

特定区域中的微小电极来影响行为、移动和其它功能。脑部刺激技术目前在美国被批准来治疗运动疾病，诸如帕金森氏病，并且正在研究用于治疗强迫症和严重的抑郁症。

[0274] 还检查了将电荷递送至神经系统的相同部分的装置，所述相同部分经由运动来激活，所述运动已知与增加的代谢相关。此类装置可以通过促进其代谢而能够帮助人们减轻体重。

[0275] 本发明的方法也可以使用药物组合物来进行，所述药物组合物包含如本文所定义的(a)卡格列净和(b)芬特明以及药学上可接受的载体。药物组合物可各自包含介于约0.1mg和1000mg之间，或其中的任何量或范围，优选地约2.5mg至500mg的卡格列净和芬特明，并且可以配成任何适合于所选给药模式的形式。载体包括必要且惰性的药用赋形剂，包括但不限于粘结剂、悬浮剂、润滑剂、矫味剂、甜味剂、防腐剂、染料和包衣。适用于口服的组合物包括固体形式，例如丸剂、片剂、囊片、胶囊剂(分别包括速释型、定时释放型和持续释放型)、颗粒剂和散剂；以及液体形式，如溶液剂、糖浆剂、酏剂、乳剂和混悬剂。可用于肠胃外给药的形式包括无菌溶液剂、乳剂和混悬剂。

[0276] 有利地，本发明的(a)卡格列净和(b)芬特明协同治疗可以单次日剂量施用，或总的日剂量可以每天两次、三次或四次的分剂量施用。此外，本发明的协同治疗的(a)卡格列净和(b)芬特明可通过局部使用合适的鼻内介质经鼻内形式施用，或通过本领域普通技术人员所熟知的透皮药贴剂施用。要以透皮递送体系的形式施用，则在整个剂量方案中剂量施用将当然是连续的而不是间断的。

[0277] 例如，对于以片剂或胶囊剂形式口服给药而言，可以将(a)卡格列净和(b)芬特明与口服、无毒性的药学上可接受的惰性载体(诸如乙醇、甘油、水等)组合。此外，在希望或必要时，也可以将合适的粘结剂、润滑剂、崩解剂和着色剂掺入到该混合物中。合适的粘结剂包括但不限于淀粉、明胶、天然糖类(例如葡萄糖或β-乳糖)、玉米甜味剂、天然树胶和合成树胶(如阿拉伯树胶、黄蓍胶)或油酸钠、硬脂酸钠、硬脂酸镁、苯甲酸钠、乙酸钠、氯化钠等。崩解剂包括但不限于淀粉、甲基纤维素、琼脂、膨润土、黄原胶等。

[0278] 液体形式在经适当矫味的悬浮剂或分散剂中，该悬浮剂或分散剂诸如合成树胶和天然树胶，例如黄蓍胶、阿拉伯树胶、甲基纤维素等。对于非肠道给药，无菌混悬剂和溶液剂是期望的。当需要进行静脉内施用时，采用通常含有合适的防腐剂的等渗制剂。

[0279] 当需要治疗抑郁症时，可将本发明的协同治疗，以及构成所述协同治疗的(a)卡格列净和(b)芬特明以任何前述组合物形式并根据本领域确立的剂量方案来施用。

[0280] 卡格列净、芬特明和/或包含卡格列净和芬特明的协同治疗的每一种的日剂量可以在每个成人每天0.01至150mg/kg的宽范围内变化。对于口服给药而言，卡格列净、芬特明和/或包含卡格列净和芬特明的协同治疗的每一种可优选以含有0.01、0.05、0.1、0.5、1.0、2.5、3.75、5.0、7.5、10.0、15.0、25.0、30.0、37.5、50.0、100、150、200、250、300、500和1000毫克的活性成分的片剂的形式提供给待治疗的患者，用于根据症状来调节剂量。有效量的活性成分通常是以每天每千克体重约0.01mg至约1500mg的剂量水平提供。优选地，该范围为每天每千克体重约0.05至约100.0mg，更优选地为每天每千克体重约0.05至约50mg，更优选地为每天每千克体重约0.05至约25.0mg。活性成分可根据每天1至4次的方案，同时、顺序或分别地或以单一剂量形式来施用。

[0281] 本领域技术人员可容易地确定待施用的最佳剂量，并且最佳剂量将随所使用的具

体化合物、施用方式、制剂强度、施用方式和疾病病症的进程而变化。此外，与接受治疗的具体患者相关的因素，包括患者年龄、体重、饮食以及施用时间，将导致需要调节剂量。

[0282] 以下实施例是为了帮助理解本发明而示出的，并非旨在且不应该被解释为以任何方式限制实施例之后的权利要求书中所示出的本发明。

[0283] 实施例1：临床试验

[0284] 具有300mg卡格列净和15mg芬特明的协同治疗

[0285] 以26周，随机、双盲、安慰剂对照、平行组、多中心研究的方式，研究具有300mg卡格列净和15mg芬特明的联合治疗的安全性和功效。(完整的研究方案提交于并作为STUDY 28431754-OBE2002在www.clinicaltrials.gov上可得)。

[0286] 试验设计：

[0287] 研究以4周单盲安慰剂导入周期开始。在完成导入周期之后，将335名超重或肥胖非糖尿病成人受检者(其在筛选时，具有≥30kg/m^2和＜50kg/m^2的BMI；或在存在高血压和/或血脂异常的一种或多种共病的情况下，在筛选时，具有≥27kg/m^2和＜50kg/m^2的BMI)，以1:1:1:1的比率随机分配，以用下列物质治疗：(A)卡格列净300mg和芬特明15mg，(B)卡格列净300mg，(C)芬特明15mg，或(D)安慰剂，其中分层因子：导入体重减轻≤2kg或＞2kg。所有受检者均提供有针对体重减轻的饮食和运动咨询(标准化非药理学治疗)，并且被指示在整个研究期间遵循饮食和运动计划。

[0288] 修改的意向性治疗(mITT)分析集包括所有随机受检者，其已经接受至少一个剂量的研究药物。主要功效端值为在第26周的体重自基线的变化百分比。次要功效端值包括：(1)在第26周体重减轻≥5％的受检者的比例，(2)在第26周SBP(静态血压)自基线的绝对变化；和(3)在第26周体重自基线的绝对变化。包含卡格列净300mg和芬特明15mg作为独立治疗组允许描述对于协同治疗卡格列净300mg/芬特明15mg组中单独组分对观察到的体重减轻的相对贡献的评价，并且提供卡格列净300mg在非糖尿病、超重/肥胖群体中的功效和安全性数据。安全性分析包括治疗突发性不良事件(在该文献中被称为不良事件)、实验室测试(包括化学和血液学)以及生命病征(血压和脉搏率)。

[0289] 将335名受检者随机化并且对334名受检者给药；334名受检者构成mITT分析集，其中231名(69％)完成研究。一名受检者在不满足资格标准之后被无意随机化，但未被给药。相比于其它治疗组，中断的受检者比例在卡格列净300mg和芬特明15mg的协同给药中较低。总体来说，失去后续追踪和不良事件是中断的最常见原因(分别为12.9％和7.5％)。没有受检者由于严重不良事件(SAE)而中断。

[0290] 大部分受检者为女性(81.7％)，白种人(78.4％)，平均年龄45.7岁，平均基线HbA_{1c}为5.6％，平均BMI为37.3kg/m^2，平均基线重量为102.9kg，平均eGFR为95.8mL/min/1.73m^2。少数受检者(27.2％)在4周导入周期内减轻多于2kg。总体来说，在整个治疗组中基线特征大体相似。

[0291] 结果：

[0292] 下表1汇总了卡格列净300mg/芬特明15mg的协同治疗相对于安慰剂对体重和收缩压(SBP)的作用。

[0293] 表1：结果：联合治疗(卡格列净300mg/芬特明15mg)相对于安慰剂(26周)

[0294]

端值	差值[b]	(95% CI)[b]	p-值[a]
体重， 自基线的变化%	-6.9	(-8.6; -5.2)	<0.001

[0295]

体重减轻 ≥5%的受检者的比例	49.1	(32.2; 66.1)	<0.001
在第26周的体重 自基线的绝对变化	-6.7	(-8.5; -4.9)	<0.001
在第26周的SBP 自基线的绝对变化	-4.2	(-7.7; -0.8)	0.015

[0296] a标称p-值

[0297] b达到体重减轻≥5%端值的比例差值;所有其它端值的LS平均值的差值

[0298] 注意:对于体重自基线的百分比变化,体重自基线的绝对变化,以及SBP自基线的变化而言,CI和p-值基于重复测量的混合模型,其包括以下固定效应:治疗、导入期间的体重减轻、探访、治疗与探访的相互作用、基线值和基线与探访的相互作用,以及作为随机效应的受检者。对于实现至少5%体重减轻而言,CI基于具有连续性校正的二项分布的正态近似;p-值基于重复测量的广义线性混合模型,其包括以下固定效果:治疗、导入期间的体重减轻、探访、治疗与探访的相互作用、治疗与亚组的相互作用、基线值和基线与探访的相互作用,以及作为随机效应的受检者。

[0299] 关于在第26周自基线的变化百分比,利用卡格列净300mg/芬特明15mg的协同治疗的治疗达到相对于安慰剂的统计学显著性(分别为-7.5%相对于0.6%,p<0.001)。如所测量的,在第26周的主要体重减轻端值在图1中,以空心符号示于观察到的体重减轻图中(作为在每个时间点时,减去安慰剂效应的平均体重减轻)。更具体地,300mg卡格列净和15mg芬特明与-6.9%的统计学显著的减去安慰剂效应的体重减轻相关。另外,在26周的端值处,没有观察到体重减轻的平台,从而指示预计体重减轻将持续超过26周。相比于安慰剂的17.5%,在协同给药组中达到至少5%减重的受检者的比例为66.7%。在协同给药组中体重减轻至少10%的受检者的比例为34.9%,相对于安慰剂组的8.8%。(因此,在第26周,研究满足FDA认为对体重管理有效的两个基准:"1年治疗之后,出现以下中的任一个:活性产品和安慰剂治疗组之间的平均体重减轻差值为至少5%,并且该差值是统计学上显著的,或者活性产品组中减轻大于或等于5%的基线体重的受检者的比例为至少35%,约两倍于安慰剂组中的比例,并且组之间的差异是统计学上显著的。)基于研究中测量的26周随时间推移的体重减轻数据,外推(指数拟合)以估计1年时的体重减轻,指示对于协同给药组而言,潜在的减去安慰剂效应的体重减轻为-8.8%,如图1中由实线示出的。

[0300] 估计关于在第26周观察到的体重减轻,芬特明单独贡献了50%,卡格列净单独贡献了18%,并且相互作用贡献了32%。

[0301] 下表2提供了研究的每个治疗组在第26周的体重自基线的变化百分比:(A)利用卡格列净300mg和芬特明15mg联合治疗,(B)卡格列净300mg,(C)芬特明15mg和(D)安慰剂。

[0302] 表2:在第26周,体重自基线的变化%

[0303]

	安慰剂 (N=82)	芬特明 15mg (N=85)	卡格列净 300mg (N=84)	卡格列净 300mg /芬特明 15mg (N=83)
基线处的重量（kg）值				
N	76	76	78	77
均值(SD)	104.00 (18.344)	102.43 (18.606)	103.33 (19.626)	100.06 (18.125)
在第 26 周自基线的变化%				
LS 均值(SE)	-0.6 (0.6)	-4.1 (0.6)	-1.9 (0.6)	-7.5 (0.6)
减去安慰剂 [a]				
p-值		<0.001	0.142	<0.001
LS 均值差(SE)		-3.5 (0.9)	-1.3 (0.9)	-6.9 (0.9)
95% CI[a]		(-5.3; -1.8)	(-3.1; 0.4)	(-8.6; -5.2)
减去芬特明 15mg[a]				
p-值				<0.001
LS 均值差(SE)				-3.4 (0.9)
95% CI[a]				(-5.1; -1.6)
减去卡格列净 300mg[a]				
p-值				<0.001
LS 均值差(SE)				-5.6 (0.9)
95% CI[a]				(-7.3; -3.8)

[0304] a成对比较:CI和p值基于重复测量的混合模型,其包括以下固定效果:治疗、导入期间的体重减轻、探访、治疗与探访的相互作用、基线值和基线与探访的相互作用,以及作为随机效应的受检者。

[0305] 注意:该表仅包括具有基线和基线后体重测量的受检者。

[0306] 类似于主要功效端值,利用MMRM分析在第26周的绝对体重自基线的变化。利用广义线性混合模型来分析类别上的次要功效端值(在第26周的体重减轻≥5%的受检者的比例),所述广义线性混合模型类似于MMRM方案,但适用于纵向二元数据,其中结果示于下表3中。

[0307] 表3:在第26周,自基线的绝对体重变化

[0308]

	安慰剂 (N=82)	芬特明 15mg (N=85)	卡格列净 300mg (N=84)	可格列净 300mg / 芬特明 15mg (N=83)
基线处的重量（kg）值				
N	76	76	78	77
均值(SD)	104.00 (18.344)	102.43 (18.606)	103.33 (19.626)	100.06 (18.125)
在第 26 周自基线的变化				
LS 均值(SE)	-0.6 (0.6)	-4.1 (0.6)	-1.9 (0.7)	-7.3 (0.6)
减去安慰剂 [a]				
p-值		<0.001	0.153	<0.001
LS 均值差(SE)		-3.5 (0.9)	-1.3 (0.9)	-6.7 (0.9)
95% CI (a)		(-5.3; -1.7)	(-3.1; 0.5)	(-8.5; -4.9)
减去芬特明 15mg[a]				
p-值				<0.001
LS 均值差(SE)				-3.2 (0.9)
95% CI (a)				(-4.9; -1.4)
减去卡格列净 300mg[a]				
p-值				<0.001
LS 均值差(SE)				-5.4 (0.9)
95% CI (a)				(-7.1; -3.6)

[0309] a成对比较:CI和p值基于重复测量的混合模型,其包括以下固定效果:治疗、导入期间的体重减轻、探访、治疗与探访的相互作用、基线值和基线与探访的相互作用,以及作为随机效应的受检者。

[0310] 注意:该表仅包括具有基线和基线后体重测量的受检者。

[0311] 除了对体重减轻的作用,在协同治疗组中也观察到-4.2mmHg(基线125mmHg)的显著的减去安慰剂的收缩压降低(在第26周SBP的绝对变化为-6.9mmHg,相对于安慰剂对照组的-2.7mmHg,p=0.015)。-1.6mmHg(基线80mmHg)的舒张压降低不是统计学上显著的。类似于主要功效端值,利用MMRM分析在第26周的收缩压自基线的变化,结果如下表4所示。

[0312] 表4:在第26周,收缩压自基线的变化

[0313]

	安慰剂 (N=82)	芬特明 15mg (N=85)	卡格列净 300mg (N=84)	卡格列净 300mg /芬特明 15mg (N=83)
收缩压（mmHg），基线处的值				
N	75	76	78	77
均值(SD)	124.22 (12.937)	124.05 (11.491)	124.81 (13.309)	125.26 (13.068)
自基线的变化				
LS 均值(SE)	-2.7 (1.3)	-1.4 (1.2)	-3.1 (1.3)	-6.9 (1.2)
减去安慰剂 [a]				
p-值		0.456	0.827	0.015
LS 均值差(SE)		1.3 (1.8)	-0.4 (1.8)	-4.2 (1.7)
95% CI (a)		(-2.1; 4.8)	(-3.9; 3.1)	(-7.7; -0.8)
减去芬特明 15mg[a]				
p-值				0.001
LS 均值差(SE)				-5.6 (1.7)
95% CI (a)				(-8.9; -2.2)
减去卡格列净 300mg[a]				
p-值				0.028
LS 均值差(SE)				-3.9 (1.7)
95% CI (a)				(-7.3; -0.4)

[0314] a成对比较:CI和p值基于重复测量的混合模型,其包括以下固定效果:治疗、导入期间的体重减轻、探访、治疗与探访的相互作用、基线值和基线与探访的相互作用,以及作为随机效应的受检者。

[0315] 注意:该表仅包括具有基线和基线后收缩压测量的受检者。

[0316] 包含芬特明15mg的治疗组也看起来在在第26周增加脉搏,与芬特明的已知效果一致(芬特明15mg和卡格列净300mg/芬特明15mg的自基线的LS均值变化(SE)分别＝4.1(1.0)bpm和3.5(0.9)bpm,相比于安慰剂组中的-0.7(1.0)bpm,和卡格列净300mg组中的0.7(1.0))。表5示出了在第26周,收缩压、舒张压和脉搏率的平均值和自基线的均值变化。

[0317] 表5:在第26周,血压、脉搏率的平均值和均值变化

[0318]

	安慰剂 (N=82)	芬特明 15mg (N=85)	卡格列净 300mg (N=84)	卡格列净 300mg /芬特明 15mg (N=83)
收缩压（mmHg）				

[0319]

N	57	60	56	63
平均基线	125.27	123.39	124.70	125.28
均值变化(SD)	-3.09 (10.967)	-1.13 (10.007)	-3.31 (11.349)	-7.08 (10.128)
(95% CI)	(-6.003; -0.184)	(-3.718; 1.452)	(-6.349; -0.270)	(-9.635; -4.534)
中值变化	-2.00	-0.33	-1.67	-6.00
(95% CI)	(-6.000; 0.333)	(-3.000; 2.000)	(-6.000; 0.000)	(-8.333; -3.667)
舒张压（mmHg）				
N	57	60	56	63
平均基线	80.15	78.54	79.26	79.35
均值变化(SD)	-1.08 (7.692)	0.55 (6.864)	-1.32 (6.779)	-2.32 (6.705)
(95% CI)	(-3.123; 0.959)	(-1.223; 2.323)	(-3.131; 0.500)	(-4.006; -0.629)
中值变化	-0.33	0.67	-1.17	-0.67
(95% CI)	(-4.000; 1.667)	(-1.667; 2.667)	(-3.333; 0.333)	(-3.333; 0.333)
脉搏率（跳动次数/分钟）				
N	57	60	56	63
平均基线	72.96	70.11	69.37	73.42
均值变化(SD)	-0.89 (7.059)	5.02 (7.568)	1.64 (6.786)	3.23 (9.800)
(95% CI)	(-2.762; 0.984)	(3.067; 6.977)	(-0.175; 3.460)	(0.760; 5.696)
中值变化	-1.00	4.67	0.83	3.67
(95% CI)	(-4.000; 1.333)	(1.667; 6.667)	(-1.000; 2.667)	(0.667; 5.333)

[0320] 注意:对于每次测量,仅包括具有基线和基线测量的受检者。

[0321] 制剂实施例1-假想例

[0322] 作为口服组合物的具体实施方案,将300mg卡格列净与15mg的芬特明与足够细分的乳糖配制在一起,以提供580mg至590mg的总量以填充0号硬胶囊。

[0323] 制剂实施例2-假想例

[0324] 作为口服组合物的具体实施方案,将300mg卡格列净与15mg的芬特明与乳糖和微晶纤维素配制在一起,以提供量为约600mg至约620mg总量的片剂。

[0325] 尽管上述说明通过提供的实施例进行说明来指出了本发明的原理,但应当理解,本发明的实践涵盖以下权利要求书及其等同形式的范围内的所有一般变型形式、改变形式和/或修改形式。

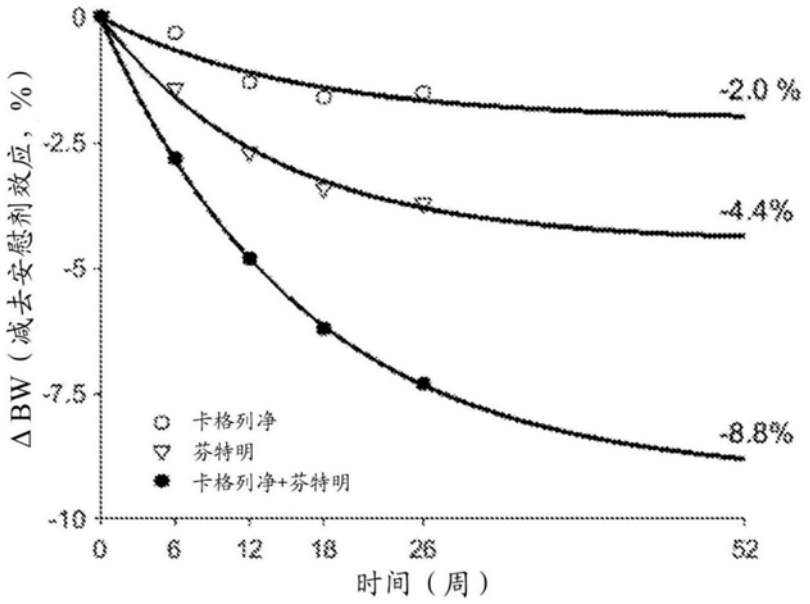


图1:卡格列净、芬特明和联合治疗的减去安慰剂效应的平均体重减轻(在0-26周,外推至52周时测量)