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(54) Title: EFFECT OF CARBOXYALKYLETHERS ON OBESITY SYMPTOMS AND LIPODYSTROPY

(57) Abstract: Methods of treating obesity symptoms, metabolic disorders or lipodystropy by administering carboxyalkylethers, in particular 6,6'-oxybis-(2,2'-dimethylhexanoic acid) or an ester, hydrate or salt thereof.

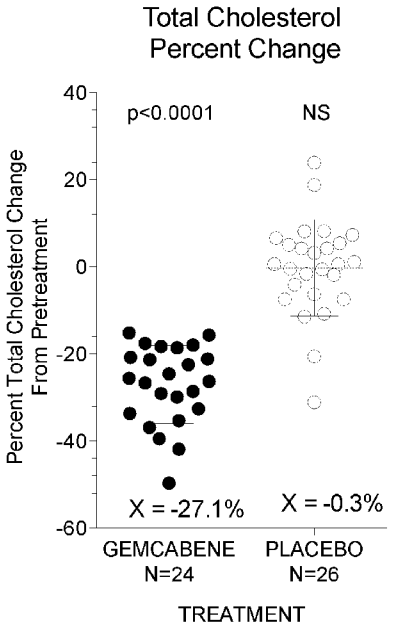

FIG. 13A

WO 2018/165120 A1

[Continued on next page]

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EFFECT OF CARBOXYALKYLETHERS ON OBESITY SYMPTOMS AND LIPODYSTROPY

PRIORITY CLAIM

[0001] This application claims priority to United States Application Serial No. 62/467,407, filed March 6, 2017,and United States Application Serial No. 62/477,831, filed March 28, 2017. The entire contents of the aforementioned applications are incorporated herein by reference.

FIELD

[0002] Use of a lipid lowering agent to lower apoC-II, apoC-III, modulate apoE, improve insulin sensitivy, improve obesity symptoms, and to treat subjects with congenital or acquired lipodystrophy.

BACKGROUND

[0003] Lipodystrophic (also known as lipoatrophy) syndromes encompass a heterogeneous group of rare disorders characterized by partial or generalized loss of adipose tissue depots. Metabolic abnormalities may also be associated with this condition. Lipodystrophic syndromes are commonly associated with hypertriglyceridemia, hepatic steatosis, and severe insulin resistance. The fact that insulin resistance and the consequent progression to diabetes can result from either obesity or lipodystrophy reflects the crucial role of adipose tissue in carbohydrate and lipid metabolism. In the absence of adequate adipocyte capacity, excess calories cannot be diverted to their normal storage depot; instead they accumulate as increased triglyceride stores in liver, in skeletal and cardiac muscle, and in the pancreatic β cell. This extra-adipose lipid accumulation, through as-yet unclear means, is associated with impaired insulin action and, often, diabetes.

[0004] Lipodystrophies are associated with partial or complete leptin deficiency. Leptin replacement therapy dramatically improves dyslipidemia, total cholesterol, insulin sensitivity, reduction in HbA1c, and intrahepatic fat content. In patients not fully responsive to anti-hyperglycemic medications or high dose insulin, leptin reduces fasting blood glucose and HbA1c levels. Studies have shown that a synthetic human leptin analogue administered over a three year period demonstrated a durable responses including reduction of glucose , triglycerides, and liver enzymes to reduce some of the abnormalities associated with lipodystrophy Ficarella et al., (Curr Diab Rep Vol. 15:12 (2015)), Handlelsman et al., (published online, Endocr Pract. Vol. 19(1): 107-116 (2013)), (Oral et al., N Engl J. Med, Vol. 346, No. 8 (2012)). United States Patent No.

7,183,254, discloses leptin, leptin analogs, and leptin derivative and methods of treating patients with lipoatrophy. United States Patent No. 7,183,254 is herein incorporated by reference in its entirety. Use of a recombinant form of leptin analog, metreleptin, was approved in 2014 as a replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. In some cases, immunogenicity (e.g., formation of neutralizing antibodies) can develop to metreleptin, reducing its effectiveness in continued treatment.

[0005] Although subcutaneous metreleptin replacement therapy can dramatically improve diabetes control, hepatic steatosis, and hypertriglyceridemia in severely hypoleptinemic patients with generalized lipodystrophy, its effects in patients with familial partial lipodystropy (FPL) so far have been less dramatic (Park et al., Metab. and Exper. Vol. 56 pp508-516 (2007)).

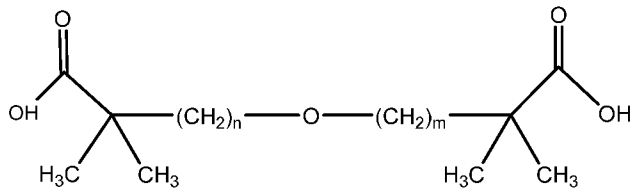
[0006] Obesity is a term that has been precisely defined by the National Institutes of Health (the NIH) as a BMI (Body Mass Index) of 30 and above. The BMI, a key index for relating body weight to height, is a person's weight in kilograms (kg) divided by their height in meters (m) squared. Since the BMI describes the body weight relative to height, it correlates strongly (in adults) with the total body fat content. Insulin sensitivity describes how sensitive the body is to the effects of insulin. Someone said to be insulin sensitive will require smaller amounts of insulin to lower blood glucose levels than someone who has low sensitivity. Low insulin sensitivity, or insulin resistance, is associated with type 2 diabetes and obesity. The insulin resistance of obesity and type 2 diabetes is often associated with a metabolic dyslipidemia that increases cardiovascular risk. Insulin resistance can impair the ability to metabolize glucose for fuel, prompting a switch from fat storage that promotes free fatty acid flux, hepatic triglyceride synthesis and increased VLDL production.

[0007] Because obesity and low insulin sensitivity is associated with negative biological effects, there is a need for additional treatments that can improve these symptoms in obese and non-diabetic subjects. Likewise there is a need for additional treatments to avoid the negative biological effects and to treat metabolic abnormalities associated with lipodystropy.

SUMMARY

[0008] In the present disclosure, the inventors have disclosed methods for treating subjects with negative biological effects of obesity (other than weight) and in subjects with lipodystrophy.

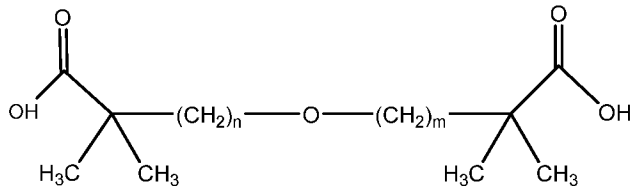
[0009] A first aspect of the present invention provides methods for increasing insulin sensitivity in a patient in need thereof comprising administering to the patient an effective amount of a compound of formula (I):



(I)

or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

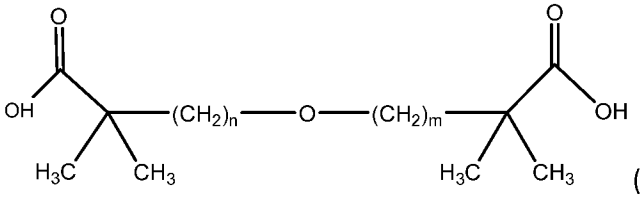
[0010] A second aspect of the present invention provides methods for decreasing blood glucose levels in a patient in need thereof comprising administering to the patient an effective amount of a compound of formula (I):



(I)

or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

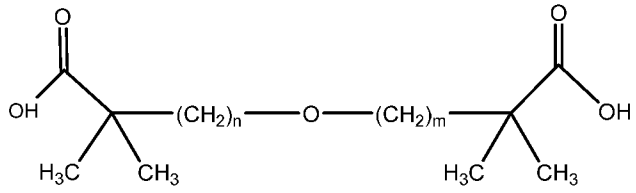
[0011] A third aspect of the present invention provides methods for decreasing HbA1c levels in a patient in need thereof comprising administering to the patient an effective amount of a compound of formula (I):



(II)

or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

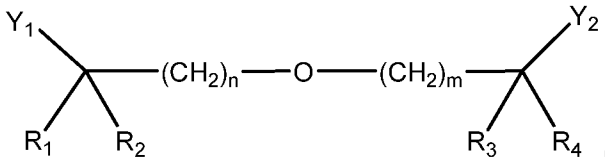
[0012] A fourth aspect of the present invention provides methods for increasing the glucose disposal rate in a patient in need thereof comprising administering to the patient an effective amount of a compound of formula (I):



(I)

or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

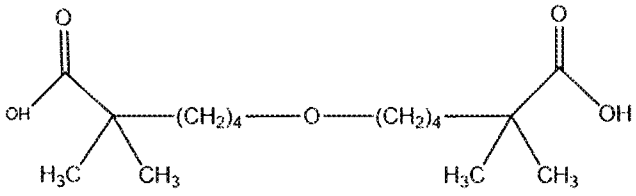
[0013] A fifth aspect of the present invention provides methods for treating lipodystrophy, comprising administering to a patient in need thereof a compound of formula II



(II)

wherein n, and m independently are integers from 2 to 9; each occurrence of R_1, R_2, R_3, and R_4 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or R_1 and R_2 taken together with the carbon to which they are attached form a carbocyclic ring having from 3 to 6 carbons, or R_3 and R_4 together with the carbon to which they are attached, form a carbocyclic ring having from 3 to 6 carbons; Y_1 and Y_2 independently are -COOH, -CHO, tetrazole, and -$COOR_5$; R_5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; or an ester, or a hydrate, or a salt thereof.

[0014] In some embodiments of the first, second, third, fourth or fifth aspect the method comprises administering the compound.



(gemcabene) or a salt or hydrate thereof.

[0015] In other embodiments of the first, second, third, fourth or fifth aspect the method comprises administering the monocalcium salt of gemcabene (gemcabene, calcium).

BRIEF DESCRIPTION OF THE FIGURES

[0016] Figures 1A (Genetic Models) and 1B (Charles River Laboratories) show the increase in plasma total cholesterol levels, over the 32 day sampling period.

[0017] Figures 2A (Genetic Models) and 2B (Charles River Laboratories) show the decrease in plasma triglycerides levels, over the 32 day sampling period.

[0018] Figures 3A (Genetic Models) and 3B (Charles River Laboratories) show the changes in plasma non-HDL-cholesterol levels, over the 32 day sampling period.

[0019] Figures 4A (Genetic Models) and 4B (Charles River Laboratories) show the increase in plasma HDL-cholesterol levels over the 32 day sampling period.

[0020] Figures 5A (Genetic Models) and 5B (Charles River Laboratories) show the increased ratio of plasma HDL-C to plasma non-HDL-C over the 32 day sampling period.

[0021] Figures 6A (Genetic Models) and6 (Charles River Laboratories) show the changes in plasma apolipoprotein A-I, E, C-II and C-III on the 32nd day of sampling.

[0022] Figures 7A (Genetic Models) and 7B (Charles River Laboratories) show the changes in fasted blood glucose levels over the 32 day sampling period.

[0023] Figures 8A (Genetic Models) and 8B (Charles River Laboratories) show the changes in fasted plasma insulin levels over the 32 day sampling period.

[0024] Figures 9A (Genetic Models) and 9B (Charles River Laboratories) show the ratio of blood fasted glucose levels/ fasted insulin levels on day 32nd day of sampling.

[0025] Figures 10A (Genetic Models) and 10B (Charles River Laboratories) show the changes in body weight over the 32 day sampling period.

[0026] Figures 11A (Genetic Models) and 11B (Charles River Laboratories) show the changes in liver weight on day 32nd day of sampling.

[0027] Figures 12A (Genetic Models) and 12B (Charles River Laboratories) show the percent liver weight to body weight on day 32nd day of sampling.

[0028] Figures 13A shows that gemcabene significantly lowered total cholesterol (TC) by a mean percentage of 27.1% ($p<0.0001$) versus placebo (0.3%) in obese human subjects after 4 weeks in treatment.

[0029] Figures 13B shows that gemcabene significantly lowered LDL-C by a mean percentage of 39.6% ($p<0.0001$) versus placebo (+0.9%) in obese human subjects after 4 weeks in treatment.

[0030] Figures 13C shows that gemcabene lowered TGs by a mean percentage of 3.2% versus placebo (2.5%) in obese human subjects after 4 weeks in treatment.

[0031] Figures 13D shows that gemcabene significantly increased percent glucose disposal rate change by mean percentage of 13.1% ($p<0.0178$) versus placebo (6.3%) in obese human subjects after 4 weeks in treatment.

DETAILED DESCRIPTION

[0032] We have discovered that treatment of patients with gemcabene may provide such a treatment to improve insulin sensitivity in obese, non-diabetic and subjects with liposdystrophy.

[0033] **Definitions**

[0034] Dose or dosing amounts refer to the amount of the parent compound even when the compound is administered as a salt, an ester or a hydrate.

[0035] ACC1 is an abbreviation for acetylCoA carboxylase I.

[0036] apoB is an abbreviation for apolipoprotein B.

[0037] apoE is an abbreviation for apolipoprotein E.

[0038] apoC-II is an abbreviation for apolipoprotein C-II.

[0039] apoC-III is an abbreviation for apolipoprotein C-III.

[0040] CRP is an abbreviation for c-reactive protein.

[0041] hsCRP is an abbreviation for high sensitivity CRP.

[0042] CGL is an abbreviation for congenital generalized lipodystrophy.

[0043] FPL is an abbreviation for familial partial lipodystropy.

[0044] AGL is an apreviation for acquired generalized lipodystrophy.

[0045] GDR is an abbreviation for average glucose disposal rate.

[0046] HDL is an abbreviation for high-density lipoprotein.

[0047] HDL-C is an abbreviation for high-density lipoprotein cholesterol.

[0048] Non-HDL-C is comprised of VLDL-C plus LDL-C, and can be calculated as Total Cholesterol minus HDL-C.

[0049] HbA1c is an abbreviation for glycated hemoglobin.

[0050] LDL is an abbreviation for low-density lipoprotein.

[0051] LDL-C is an abbreviation for low-density lipoprotein cholesterol.

[0052] An obese person has a BMI (Body Mass Index) of 30 and above. BMI is a person's weight in kilograms (kg) divided by their height in meters (m) squared. A person with obesity is the same as an obese person.

[0053] Patient and subject are used interchangeably herein to refer to a human, unless clearly indicated otherwise.

[0054] The terms symptoms and complications are used interchangeably herein.

[0055] TC is an abbreviation for total cholesterol.

[0056] TG is an abbreviation for triglyceride.

[0057] The terms "treatment" or "treating" include therapeutic treatment and prophylactic treatment. Therapeutic treatment is treatment of a subject that has signs or symptoms of the disease, condition or disorder to be treated. Prophylactic treatments refers to treatment of a subject that is predisposed to the disease, condition or disorder that does not show overt signs of the disease, condition or disorder.

[0058] Throughout the description and claims of this specification the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

[0059] As used herein, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise.

[0060] As used herein, "alkyl" refers to a saturated aliphatic hydrocarbon containing 1-6 carbon atoms. An alkyl can be straight or branched.

[0061] As used herein, "alkenyl" refers to an aliphatic carbon that contains 2-6 carbon atoms and at least one double bond. Like an alkyl, an alkenyl can be straight or branched.

[0062] As used herein, "alkynyl" refers to an aliphatic carbon that contains 2-6 carbon atoms and at least one triple bond. Like an alkyl, an alkynyl can be straight or branched.

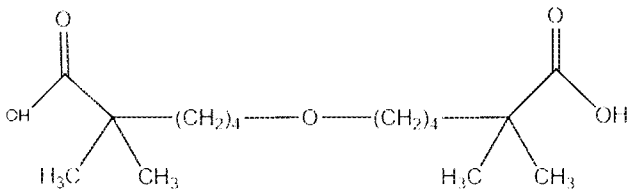
[0063] The term "carbocyclic ring" encompasses cycloalkyl and cycloalkenyl rings having 3-7 carbons. Carbocyclic rings can be optionally substituted with one or more substituents such as aliphatic (e.g., alkyl, alkenyl, or alkynyl).

[0064] VLDL is an abbreviation for very low-density lipoprotein.

[0065] VLDL-C is an abbreviation for very low-density lipoprotein cholesterol.

[0066] Gemcabene, an apoC-III and CRP modulator, has been shown to significant for LDL-C, ApoB, TG and hsCRP lowering and trends of glucose lowering in dyslipidemic subjects. In preclinical studies, 3T3L1 differentiated adipocytes treated with either 100μM gemcabene plus insulin or 100μM 7,7'-oxybis(2,2-dimethylheptanoic acid) plus insulin resulted in about a 25% and 100 % increase in [14C] deoxyglucose uptake, respectively, compared to about 70% increase with 5 μM troglitazone and insulin, suggesting possible insulin sensitization by gemcabene and other related compounds. To further investigate these observations, we assessed effect of gemcabene on average glucose disposal rate (GDR) during the last 30 minutes of a 3-hour euglycemic hyperinsulinemic clamp in healthy, obese, non-diabetic human patients before Day 1 and after 4 weeks of 900 mg once daily gemcabene after 4 weeks or once daily placebo treatment. The pretreatment GDR and posttreatment GDR was compared by paired analysis for both the gemcabene and placebo treatment groups.

[0067] Gemcabene has the formula:



and is generally administered at the monocalcium salt, (gemcabene, calcium). The term "Gemcabene, calcium" has been shortened to gemcabene when used in various publications describing clinical trials or data. "Gemcabene, calcium" is also known as gemcabene and PD72953-0038. The term "PD72953" is also known as PD72953-0000, and is the diacid form of "Gemcabene, calcium".

[0068] Gemcabene has a dual mechanism of action that involves: (1) enhancing the clearance of VLDL; and (2) blocking the overall production of hepatic TG and cholesterol synthesis.

[0069] In addition, gemcabene may have an effect on inflammation by reducing CRP mRNA production and decreasing high sensitivity CRP (hsCRP). Gemcabene decreases the expression level of apolipoprotein C-III (apoC-III) mRNA likely resulting in decreased apoC-III protein production. Gemcabene reduction in apoC-III increases VLDL-remnant clearance and enhances lipoprotein lipase activity, with the overall effect of reducing VLDL particle number and production of low-density lipoprotein (LDL). Reduction of apoC-II is also associated with increase clearance of TG-rich lipoproteins, however its reduction is also associated with decreased activation of lipoprotein lipase. Therefore, some reduction in apoC-II is expected to decrease plasma TG, however, too much reduction in apoC-II is expected to inhibit activation of lipoprotein lipase and impede the reduction of plasma TG. In primary rat hepatocytes, gemcabene markedly blocked radiolabeled acetate incorporation into both TG and cholesterol. Cytoplasmic acetylCoA carboxylase (ACC1) is the rate-limiting step in de novo fatty acid synthesis that catalyzes the conversion of acetylCoA to malonylCoA. Gemcabene's inhibition of human recombinant ACC1 enzymatic activity suggests it may block this rate-limiting step of de novo fatty acid synthesis. In stretozotocin-induced diabetes in mice fed a high-fat high caloric diet, gemcabene reduced hepatic ACC1 mRNA levels. In addition, gemcabene may have an effect on inflammation by reducing CRP mRNA production and decreasing CRP. Taken together, gemcabene's mechanism of action should lower several parameters (atherogenic particles [VLDL, VLDL remnants and LDL] and inflammation) associated with the pathology of metabolic syndrome. Gemcabene targets multiple pathways and should be helpful in treating obesity symptoms and lipodystropy symptoms.

[0070] Lipodystrophy can generally be classified on the basis of the extent or pattern of fat loss (generalized or partial) as well as whether the disease is genetic (i.e. the tendency to lose fat is present at birth) or acquired (the loss of fat occurs later in life). The major lipodystrophy subtypes are congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPL), and acquired generalized lipodystrophy (AGL). Human immunodeficiency virus (HIV)-associated lipodystrophy has been categorized as a type of AGL. There is more than one genetic form of lipoatrophy. For example, mutations in the gene encoding lamin A/C (LMNA) has been shown to be associated with the Dunnigan-type familial partial lipodystrophy (FPL). Individuals with Dunnigan's FPL are born with a normal fat distribution, but at puberty, they develop progressive subcutaneous extremity and truncal fat loss, with sparing of visceral and head and neck adipose tissue. A different chromosomal location (9q34) has also been linked to a disease gene for congenital generalized lipodystrophy). Congenital generalized lipodystrophy is a

recessive disorder characterized by a near complete absence of adipose tissue from birth, insulin resistance, hypertriglyceridemia and acanthosis nigricans.

[0071] Patients infected with HIV and are treated with highly active antiretroviral therapy (HAART) develop a partial lipodystrophy, characterized by loss of subcutaneous fat from the face, extremities and trunk, with increased visceral fat and a `buffalo hump' similar to that seen in Cushing's syndrome. These patients may also develop metabolic disorders such as insulin resistance and hypertriglyceridemia. Acquired forms of lipodystrophy may also be associated with juvenile dermamyositis and other autoimmune diseases.

[0072] Investigations in animal models have demonstrated that these metabolic abnormalities may be associated with fat loss. But insulin resistance and hypertriglyceridemia that characterize lipoatrophy have been extremely refractory to treatment, even though a variety of approaches have been tried. One of these approaches includes treatment with thiazolidinediones, which are PPARγ (peroxisome proliferator activated receptor gamma) agonists. While thiazolidinediones are appealing because they promote both adipocyte differentiation and insulin sensitivity, patients receiving thiazolidinediones are usually managed with combination therapy, including high dose insulin, oral hypoglycemic agents (e.g. metformin and thiazolidinediones), and lipid-lowering drugs, (e.g., fibrates and statins). Despite these therapies, patients with generalized lipoatrophy continue to manifest severe hypertriglyceridemia (which causes recurrent attacks of acute pancreatitis), severe hyperglycemia (which poses risk of diabetic retinopathy and nephropathy), and non¬alcoholic steatohepatitis (which can result in cirrhosis). In fact, one member of the thiazolidinediones, troglitazone, was removed from the US market because of its rare but severe hepatotoxicity, leaving two thiazolidinediones (rosiglitazone and pioglitazone) available. Patients are also treated with fibrates, niacin and sometimes statins. However, treatment of these patients with statins is usually not an option as they are generally intolerant of statins.

[0073] A variety of genetically engineered animal models for lipoatrophy have been developed and tested. These models, however, provide conflicting results as to the sensitivity of these animals to treatment with leptin. For example, in one transgenic mouse model, which expresses a truncated nuclear version of SREBP-1 c and mimics the features of congenital generalized lipodystrophy having insulin resistance and markedly low adipose tissue, continuous systemic infusion of leptin overcame the resistance of the mice to insulin. On the other hand, a different transgenic mouse, which expresses the A-ZIP/F-1 gene and characterized by lack of fat tissue, severe resistance to insulin, diabetes, and greatly reduced serum leptin levels, failed to respond to leptin at similar doses and were minimally effective at higher doses. Any efficacy

with leptin also diminished with age of the animal. Furthermore, although insulin resistance was overcome with leptin in the SREBP-lc transgenic mice, reversal of lipodystrophy was not observed.

[0074] Although in human trials with patients having generalized lipodystrophy, leptin therapy dramatically decreased plasma triglycerides by 60% (95% confidence interval 43-77%) and liver volume by 28% (95% confidence interval 20-36%) in diabetic lipodystrophy patients. Leptin therapy led to a large reduction or discontinuation of anti-diabetic medication, although fasting triglycerides were still elevated after 4 months, whereby 6 out of 9 patients still had fasting TG>200mg/dL and one patient had a level of 1214 mg/dL Furthermore, even with leptin therapy, the day to day variability in triglyceride can easily fluctuate by as much as about 1000 mg/dL (Oral et al., N Engl J. Med, Vol. 346, No. 8 (2012)).

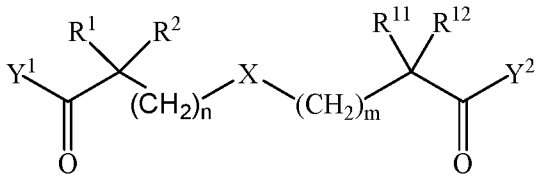
[0075] Familial partial lipodystrophy (FPL) is a rare genetic disorder characterized by selective, progressive loss of body fat (adipose tissue) from various areas of the body. Individuals with FPL often have reduced subcutaneous fat in the arms and legs and the head and trunk regions may or may not have loss of fat. Conversely, affected individuals may also have excess subcutaneous fat accumulation in other areas of the body, especially the neck, face and intra-abdominal regions. Subcutaneous fat is the fatty or adipose tissue layer that lies directly beneath the skin. In most cases, adipose tissue loss begins during puberty. FPL can be associated with a variety of metabolic abnormalities. The extent of adipose tissue loss usually determines the severity of the associated metabolic complications. These complications can include an inability to properly breakdown a simple sugar known as glucose (glucose intolerance), elevated levels of triglycerides (fat) in the blood (hypertriglyceridemia), and diabetes. Additional findings can occur in some cases. Six different subtypes of FPL have been identified. Each subtype is caused by a mutation in a different gene. The subdivisions of FPL are autosomal recessive, FPL type 1 (Kobberling lipodystrophy), FPL type 2 (Dunnigan lipodystropy), FPL type 3, FPL type 4 and FPL type 5. Four forms of FPL are inherited as autosomal dominant traits; one form is inherited as an autosomal recessive trait. The mode of inheritance of FPL, Kobberling variety is unknown.

[0076] Common symptoms of FPL include selective, progressive loss of subcutaneous fat in the arms and legs and chest and trunk regions, abnormal accumulation of subcutaneous fat in other areas, and a variety of metabolic complications. Generally, women are more severely affected than men by the metabolic complications of FPL. Additional symptoms including those affecting the liver or heart may also occur.

[0077] In some embodiments the compound of formula I or formula II is administered at a dose from about 25 mg to about 900 mg daily. In some embodiments the dose of gemcabene is 25 mg, 50 mg, 75 mg, 150 mg, 300 mg, 450 mg, 600 mg or 900 mg. In some embodiments the dose of gemcabene is 150 mg, 300 mg, 600 mg or 900 mg. In some embodiments the dose of gemcabene is 300 mg, 600 mg or 900 mg. In some embodiments the daily dose of gemcabene is 25 mg, 50 mg, 75 mg, 150 mg, 300 mg, 450 mg, 600 mg or 900 mg. In some embodiments the daily dose of gemcabene is 150 mg, 300 mg, 600 mg or 900 mg. In some embodiments the daily dose of gemcabene is 300 mg, 600 mg or 900 mg.

[0078] In some embodiments the compound of formula I or formula II may be administered 1, 2, 3, or 4 times per day. Preferably the gemcabene is administered 1 or 2 times a day. More preferably gemcabene is administered 1 time per day.

[0079] In some embodiments the compound is for lower apoC-II, apoC-III, modulate apoE, improve insulin sensitivy, improve obesity symptoms, and to treat subjects with congenital or acquired lipodystrophy, in particular FPL, is a compound of formula III



(III) or a pharmaceutically acceptable salt, or hydrate, wherein

m is an integer from 0 to 5;

n is an integer from 3 to 7;

X is $-(CH_2)_z-$, –O-, –CH(OH)-, $CH(CH_2OH)$-, -NH- or –S-, wherein z is an integer from 0 to 4;

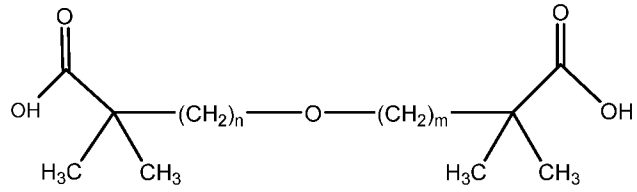
each occurrence of R^1 and R^2 is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, benzyl, or R^1 and R^2 and the carbon to which they are both attached are taken together to form a $(C_3\text{-}C_7)$cycloakyl group;

each occurrence of R^{11} and R^{12} is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, benzyl, or R^{11} and R^{12} and the carbon to which they are both attached are taken together to form a $(C_3\text{-}C_7)$cycloakyl group;

each occurrence of Y^1 and Y^2 is independently $(C_1–C_6)$alkyl, OH, COOH, $COOR^3$; and

R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups.

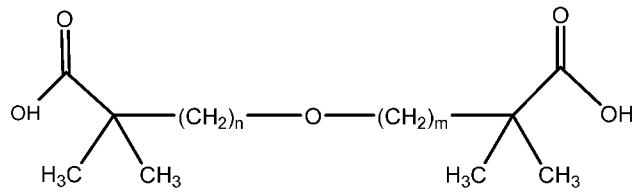
[0080] A first embodiment of the present invention provides a method for increasing insulin sensitivity in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of formula (I):



(I)

or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

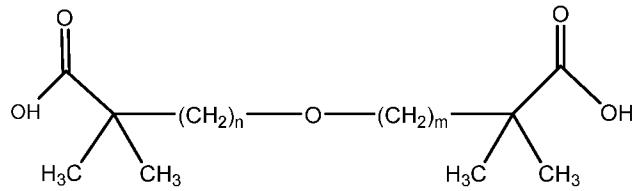
[0081] A second embodiment of the present invention provides a method for decreasing blood glucose levels in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of formula (I):



(I)

or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

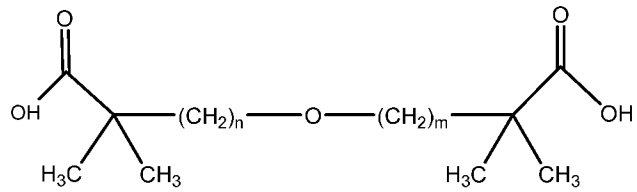
[0082] A third embodiment of the present invention provides a method for decreasing HbA1c levels in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of formula (I):



(I)

or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

[0083] A fourth embodiment of the present invention provides a method for increasing the glucose disposal rate in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of formula (I):



(I)

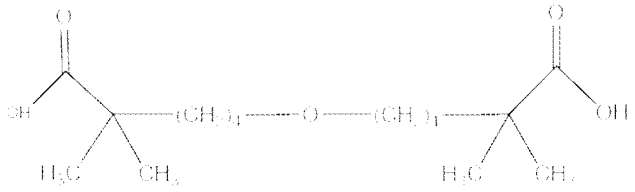
or a salt, or hydrate thereof, wherein n and m are each independently the integer 3, 4, 5, or 6.

[0084] The fifth embodiment is the method according to any one of embodiments 1-4, wherein m and n are the same integer.

[0085] The sixth embodiment is the method according to any one of embodiments 1-4, wherein m and n are different integers.

[0086] The seventh embodiment is the method according to any one of embodiments 1-4, wherein m and n are each 5.

[0087] The eighth embodiment is the method according to any one of embodiments 1-4, wherein the compound of formula (I) is



(gemcabene)

or a salt, or a hydrate thereof.

[0088] The ninth embodiment is the method according to embodiment 8 wherein the compound is the calcium salt of gemcabene.

[0089] The tenth embodiment is the method according to embodiment 8 wherein the compound is gemcabene, calcium.

[0090] The eleventh embodiment is the method according to any one of embodiments 1-10, wherein compound is administered to the patient in a dose from about 25 mg to about 900 mg.

[0091] The twelfth embodiment is the method of embodiment 11, wherein the dose is 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, 450 mg, 600 mg, or 900 mg.

[0092] The thirteenth embodiment is the method of embodiment 12, wherein the dose is 100 mg, 300 mg, 450 mg, 600 mg, or 900 mg. Or the dose administered is 300 mg, 600 mg or 900 mg.

[0093] The fourteen embodiment is the method according to any one of embodiments 8-13, wherein the dose is administered to the patient once daily.

[0094] The fifteenth embodiment is the method according to any one of embodiments 1-14, wherein the patient is obese and not diabetic.

[0095] The sixteenth embodiment is the method according to any one of embodiments 1-15, wherein the patient is above normal body weight for height.

[0096] The seventeenth embodiment is the method according to any one of embodiments 1-16, where the patient is at risk for developing diabetes.

[0097] The eighteenth embodiment is the method according to any one of embodiments 1-17, where the patient has impaired glucose tolerance.

[0098] The nineteenth embodiment is the method according to any one of embodiments 1-17, wherein the glucose tolerance of the patient is improved.

[0099] The twentieth embodiment is the method according to any one of embodiments 1-14, 16, or 19, wherein the patient is diabetic.

[00100] The twenty-first embodiment is the method according to any one of embodiments 1-20, wherein the compound is administered with an additional therapeutic agent.

[00101] The twenty-second embodiment is the method according to embodiment 21, wherein the additional agent is a glycemic control agent.

[00102] The twenty-third embodiment is the method according to embodiment 22, wherein the glycemic control agent is administered orally.

[00103] The twenty-fourth embodiment is the method according to embodiment 22, wherein the glycemic control agent is administered subcutaneously.

[00104] The twenty-fifth embodiment is the method according to embodiment 22, wherein the glycemic control agent is administered intramuscularly.

[00105] The twenty-sixth embodiment is the method according to embodiment 22, wherein the glycemic control agent is administered intravenously.

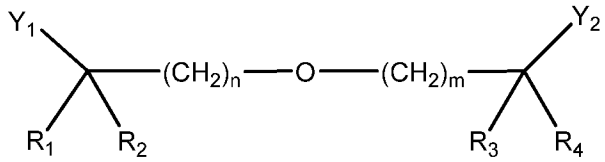
[00106] The twenty-seventh embodiment is the method of embodiment 22, where the glycemic control agent comprises one of more of insulin, a modified insulin, a short acting insulin, a long acting insulin, a basal insulin, a bolus insulin, a glucagon-like protein 1 agonist, a meglitinide, a DPP-IV inhibitor, metformin, a sulfonylurea, an alpha-glucosidase inhibitor, a sodium glucose co-transporter 2 (SGLT2) inhibitor.

[00107] The twenty-eighth embodiment is the method of embodiment 22, where the glycemic control agent is a thiazolidinedione.

[00108] The twenty-ninth embodiment is the method according to any one of embodiments 1-28, where the insulin sensitivity is improved.

[00109] The thirtieth embodiment is the method of embodiment 22, wherein the dose of the glycemic control agent administered to a patient in combination with a compound of Formula (1) is lower than the dose of the glycemic control agent is administered without the compound of Formula (1)to achieve a similar dynamic, biological or glycemic control effect.

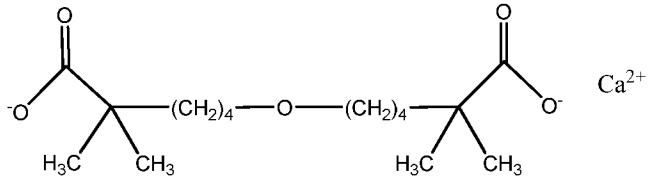
[00110] The thirty-first embodiment is the method for treating lipodystrophy, comprising administering to a patient in need thereof a compound of formula II



(II)

wherein n, and m independently are integers from 2 to 9; each occurrence of R_1, R_2, R_3, and R_4 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or R_1 and R_2 taken together with the carbon to which they are attached form a carbocyclic ring having from 3 to 6 carbons, or R_3 and R_4 together with the carbon to which they are attached, form a carbocyclic ring having from 3 to 6 carbons; Y_1 and Y_2 independently are -COOH, -CHO, tetrazole, and -$COOR_5$; R_5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; or an ester, or a hydrate, or a salt thereof.

[00111] The thirty-second embodiment is the method of embodiment 31, wherein the compound of formula II is



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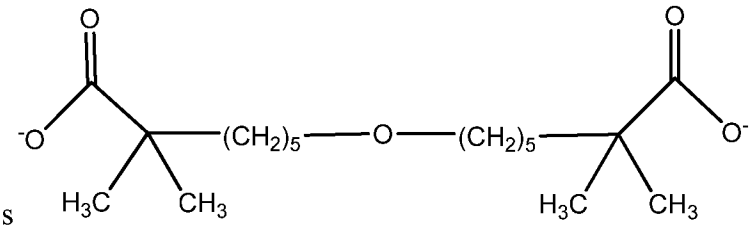
[00112] The thirty third embodiment is the method of embodiment 31, wherein the compound of formula II is



or an ester, or a hydrate or a salt thereof.

[00113] The thirty-forth embodiment is the method of any one of embodiments 31-33, wherein the lipodystrophy is a familial partial lipodystrophy.

[00114] The thirty-fifth embodiment is the method of any one of embodiments 31-34, wherein the compound of formula II is administered with an additional agent.

[00115] The thirty-sixth embodiment is the method of embodiment 35, wherein the additional agent is leptin, a leptin analog, a leptin derivative, insulin, a fibrate, a thiazolidinedione, niacin, a niacin derivative, Eicosapentenoic acid (20:5), an ester of Eicosapentenoic acid, a prodrug of Eicosapentanoic acid, metformin, a statin, an oral hypoglycemic agent, an injectable hypoglycemic agent, an apo C-III antisense molecule, an apoC-III DNAi, an apoC-III siRNA, fish oil, a PCSK9 inhibitor, a cholesterol absorption inhibitor, a bile acid sequestrant, an appetite suppressing agent, or an anti-hypertensive agent.

[00116] The thirty-seventh embodiment is the method of embodiment 36, wherein the fibrate is gemfibrozil, fenofibric acid, bezafibrate, or clofibrate.

[00117] The thirty-eigth embodiment is the method of embodiment 36, wherein the thiazolidinedione is rosiglitazone or pioglitazone.

[00118] The thirty-ninth embodiment is the method of embodiment 36, wherein the statin is atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or pitavastatin.

[00119] The fortieth embodiment is the method of embodiment 36, wherein the cholesterol absorption inhibitor is ezetimibe.

[00120] The forty-first embodiment is the method of embodiment 36, wherein the leptin analog is metreleptin.

[00121] The forty-second embodiment is the method of embodiment 36, wherein the anti-hypertensive agent is a calcium channel blocker, an ACE inhibitor, a beta-blocker, an angiotensin II receptor blocker, an alpha-2 receptor agonist, a vasodilator or a diuretic.

[00122] The forty-third embodiment is the method of embodiment 36, wherein the additional agent is an oral hypoglycemic agent and the oral agent is a biguanide , a sulfonylurea, a thiazolidinedione, a meglitimide, a D-phenylalanine derivative, an alpha-glucosidase inhibitor, a bile acid sequestrant, an insulin secretagogue, a DPP-4 inhibitor, or a combination thereof.

[00123] The forty-forth embodiment is the method of embodiment 36, wherein the additional agent is an injectable hypoglycemic agent and the injectable hypoglycemic agent is leptin, a leptin analogue, a leptin derivative, insulin, an insulin analog, an insulin derivative, amylin, a synthetic amylin, an amylin analogue, a glucagon-like peptide-1 (GLP-1), a GLP-1 analog, or a GLP-1 derivative, or a combination thereof.

[00124] The forty-fifth embodiment is the method of embodiment 44, wherein the amylin analogue is pramlintide or exenatide.

[00125] The forty-sixth embodiment is the method of any one of 31-45, wherein the insulin sensitivity of the patient is increased.

[00126] The forty-seventh embodiment is the method of any one of 31-45, wherein the patient requires less insulin to maintain glycemic control after administration of the compound of formula II when compared with the amount of insulin required prior to administration of the compound of formula II or an ester, or a hydrate, or a salt thereof.

[00127] The forty-eighth embodiment is a method of lowering the level of plasma apoC-III in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00128] The forty-ninth embodiment is a method of lowering the level of plasma triglyceride in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00129] The fiftieth embodiment is a method of preventing pancreatitis in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00130] The fifty-first embodiment is the method of reducing the incidence of pancreatitis in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00131] The fifty-second embodiment is a method of lowering plasma VLDL-C in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00132] The fifty-third embodiment is a method of lowering plasma LDL-C in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00133] The fifty-fourth embodiment is a method of elevating plasma HDL-C in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00134] The fifty-fifth embodiment is a method of lowering non-HDL-C in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00135] The fifty-sixth embodiment is a method of lowering inflammation in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00136] The fifty-seventh embodiment is a method of treating, reducing, and prevention of medical complications in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00137] The fifty-eighth embodiment is a method of treating, reducing, and prevention of cardiovascular disease in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00138] The fifty-ninth embodiment is a method of treating, reducing, and prevention of inflammatory conditions or disease in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00139] The sixtieth embodiment is a method of treating, reducing, and prevention of abnormal redistribution of body fat in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00140] The sixty-first embodiment is a method of treating, reducing, and prevention of body weight gain in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00141] The sixty-second embodiment is a method of treating, reducing, and prevention acanthosis nigricans in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00142] The sixty-third embodiment is a method of delaying the time of onset or the severity of symptoms of FPL in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00143] The sixty-forth embodiment is a method of treating, reducing the incidence of, or preventing hyperphagia in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof.

[00144] The sixty-fifth embodiment is the method of any one of embodiments 48-64, wherein the compound of formula II is administered with an additional agent.

[00145] The sixty-sixth embodiment is the method of embodiment 65, wherein the additional agent is leptin, a leptin analog, a leptin derivative, insulin, a fibrate, a thiazolidinedione, niacin, a niacin derivative, Eicosapentenoic acid (20:5), an ester of Eicosapentenoic acid, a prodrug of Eicosapentenoic acid, metformin, a statin, an oral hypoglycemic agent, an injectable hypoglycemic agent, an apo C-III antisense molecule, an apoC-III DNAi, an apoC-III siRNA, fish oil, a PCSK9 inhibitor, a cholesterol absorption inhibitor, a bile acid sequestrant, an appetite suppressing agent, or an anti-hypertensive agent.

[00146] The sixty-seventh embodiment is the method of embodiment 66, wherein the fibrate is gemfibrozil, fenofibric acid, bezafibrate, or clofibrate.

[00147] The sixty-eighth embodiment is the method of embodiment 66, wherein the thiazolidinedione is rosiglitazone or pioglitazone.

[00148] The sixty-ninth embodiment is the method of embodiment 66, wherein the statin is atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or pitavastatin.

[00149] The seventieth embodiment is the method of embodiment 66, wherein the cholesterol absorption inhibitor is ezetimibe.

[00150] The seventy-first embodiment is the method of embodiment 66, wherein the leptin is metreleptin.

[00151] The seventy-second embodiment is the method of any one of embodiments 31 or 34-71, wherein the compound is a compound of formula II, wherein n is 2, or n is 3, or n is 4, or n is 5, or n is 6, or n is 7, or n is 8, or n is 9. In some embodiments, m is 2, or n is 3, or m is 4, or m is 5, or m is 6, or m is 7, or m is 8, or m is 9. In some embodiments, n and m are both 2, or n and m are both 3, or n and m are both 4, or n and m are both 5, or n and m are both 6, or n and m are both 7, or n and m are both 8, or n and m are both 9.

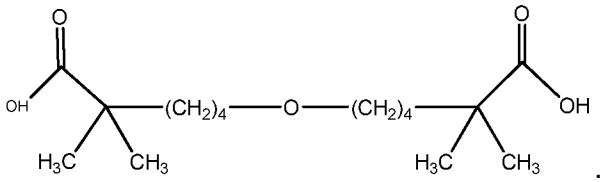
[00152] The seventy-third embodiment is the method of any one of embodiments 31 or 34-72, wherein the compound is a compound of formula II, wherein R_1, R_2, R_3, and R_4 independently are C_1-C_6 alkyl. In some embodiments R_1, R_2, R_3, and R_4 are all C_1-C_6 alkyl. In some embodiments R_1, R_2, R_3, and R_4 independently are C_2-C_6 alkenyl. In some embodiments R_1, R_2, R_3, and R_4 independently are C_2-C_6 alkynyl. In some embodiments R_1, R_2, R_3, and R_4 are -CH_3. In some embodiments R_1, R_2, R_3, and R_4 are –CH_2CH_3. In some embodiments R_1, R_2, R_3, and R_4 are –$CH_2CH_2CH_3$. In some embodiments R_1, R_2, R_3, and R_4 are all C_2-C_6 alkenyl. In some embodiments R_1, R_2, R_3, and R_4 are all C_2-C_6 alkynyl. In some embodiments R_1 and R_2 taken together with the carbon to which they are attached form a carbocyclic ring having from 3 to 6 carbons. In other embodiments R_3 and R_4 together with the carbon to which they are attached, form a carbocyclic ring having from 3 to 6 carbons.

[00153] The seventy-forth embodiment is the method of any one of embodiments 31 or 34-73, wherein the compound is a compound of formula II, wherein Y_1 and Y_2 are both –COOH. In some embodiments Y_1 and Y_2 are both –CHO. In some embodiments Y_1 and Y_2 are both –tetrazole. In some embodiments Y_1 and Y_2 are both CH_2(OH). In some embodiments Y_1 and Y_2 are both -$COOR_5$ and R_5 is C_1-C_6 alkyl. In some embodiments Y_1 and Y_2 are both -$COOR_5$ and R_5 is C_2-C_6 alkenyl. In some embodiments Y_1 and Y_2 are both -$COOR_5$ and R_5 is C_2-C_6 alkynyl.

[00154] The seventy-fifth embodiment is the method of any one of embodiments 31 or 34-74, the compound is a compound formula II, wherein n an m are the same integer, and R_1, R_2, R_3, and R_4 independently are C_1-C_6 alkyl. In yet another embodiment, the compound is a compound of formula I, wherein Y_1 and Y_2 are the same and are -COOH or -$COOR_5$, and R_5 is C_1-C_6 alkyl. In a preferred embodiment, the compound is a compound formula II, wherein Y_1 and Y_2 are COOH, R_1, R_2, R_3, and R_4 are methyl, and n and m are the same and are an integer selected from 2, 3, 4, or 5, preferably n and m are the same and are 4 or 5. Most preferably n and m are 4. In still another embodiment, the compound is a compound of formula II, wherein Y_1 and Y_2 are -COOH, and R_1, R_2, R_3, and R_4 independently are C_1-C_6 alkyl, and n and m are 4. In another embodiment the compound is a compound of formula II, wherein Y_1 and Y_2 are -COOH, n and m are 4, R_1, R_2, R_3, and R_4 are methyl. In another embodiment the compound is a compound of

formula II, wherein Y_1 and Y_2 are -COOH, n and m are 5, R_1, R_2, R_3, and R_4 are methyl. In yet another embodiment, the compound is a compound of formula II, wherein Y_1 and Y_2 are –CH_2OH, and n and m are 4. In another embodiment, the compound is a compound of formula II, wherein Y_1 and Y_2 are –CH_2OH, n and m are 4 and R_1, R_2, R_3, and R_4 are methyl.

[00155] The seventy-sixth embodiment is the method of any one of embodiments 31 or 34-75, wherein the compound of formula II is 6,6'-oxybis-(2,2'-dimethylhexanoic acid) also referred to herein in as gemcabene, the structure of which is shown below



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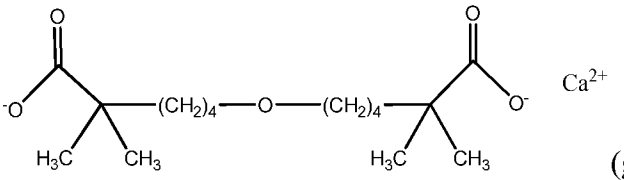
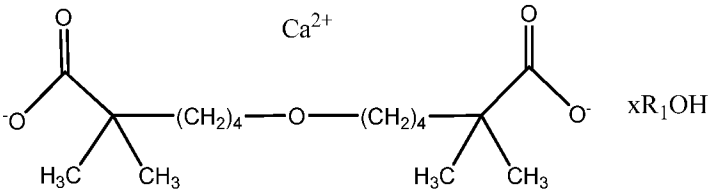
[00156] The seventy-seventh embodiment is the method of any one of embodiments 31 or 34-75, wherein the compound of formula II is the anhydrous monocalcium salt of gemcabene (gemcabene calcium):



(gemcabene calcium).

[00157] The seventy-eighth embodiment is the method of any one of embodiments 31 or 34-75, wherein compound of formula II is the hydrate of the monocalcium salt, as described in U.S. Patent No. 7,141,608 which is hereby incorporated in its entirety. The structure of the hydrate of the monocalcium salt of gemcabene is:



wherein x is an integer from 1 to 10.

[00158] The seventy-ninth embodiment is the method of any one of embodiments 31 or 34-75, wherein gemcabene calcium is administered as a crystalline form as described in U.S. Patent No. 6,861,555, which is hereby incorporated in its entirety.

[00159] The eightieth embodiment is the method according to any one of embodiments 31-79, wherein compound is administered to the patient in a dose from about 25 mg to about 900 mg.

[00160] The eight-first embodiment is the method of embodiment 80, wherein the dose is 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, 450 mg, 600 mg, or 900 mg.

[00161] The eight-second embodiment is the method of embodiment 80, wherein the dose is 100 mg, 300 mg, 450 mg, 600 mg, or 900 mg. Or the dose administered is 300 mg, 600 mg or 900 mg.

[00162] The eight-third embodiment is the method according to any one of embodiments 80-82, wherein the dose is administered to the patient once daily.

EXAMPLES

[00163] Example 1 Preclinical Studies in Female Obese Zucker rats

[00164] Metabolic syndrome associated with type 2 diabetes includes low HDL, elevated VLDL-C and TGs, insulin resistance and elevated glucose. As the metabolic syndrome condition develops temporally, a transition period is sustained whereby increasing amounts of insulin are produced to maintain baseline glucose levels. Animals were evaluated in two separate strains of female obse Zucker rats from separate vendors, Genetic Models and Charles River Laboratories. These rat models are deficient in the leptin receptor and develop age-dependent obesity and diabetes. Animals were treated once daily with either a carboxymethyl cellulose/Tween 20 vehicle or the indicated amounts of gemcabene in this vehicle. Gemcabene produced significant changes of the evaluated variables.

[00165] Methods

[00166] Female, 8-week old, obese Zucker rats from 2 sources (Genetic Models, Inc, Indianapolis, Indiana, or Charles River, Wilmington, Massachusetts), were housed 3 animals per cage. Each test group,including control, had six animals. Animals were maintained on pelleted rodent chow (Ralston Purina) and water ad lib in temperature controlled rooms on a 12-hour light/12-hour dark cycle (lights on at 6 AM). The lights were inadvertently left on continuously for the first 6 days of the study. Gemcabene was administered daily between 8 AM and 9 AM by oral gavage in a 1.5% carboxymethylcellulose plus 0.2% Tween-20 vehicle for 32 days. Rats were dosed by oral gavage with 2.5 mL/kg suspensions of vehicle alone or gemcabene (10, 30, or 100 mg/kg). On Days 0, 7, 14, 21, 28, and 32, food was removed at 7:30 AM. Animals were dosed, and a drop of blood was taken after 1 PM from the tail vein for the determination of blood glucose by an Accu-Chek Advantage Blood Glucose Monitor (Boehringer Mannheim, Indianapolis, Indiana). Glucose tolerance tests were performed on Days 14 and 21 following an oral gavage of 1 mL of 70% glucose (blood sampled at 0, 35, 70, and 140 minutes post load). Bloods from restrained animals were taken after 1 PM from the tail vein on Days 0, 7, and 21 for determining plasma lipid levels and plasma lipoprotein cholesterol distribution. On Day 32 blood samples were taken after 1 PM by cardiac puncture under Ketamine:Rompun (4:1) anesthesia. Plasma insulin was determined

by a rat insulin radioimmunoassay (RI13K, Linco Co, St Louis, Missouri). Apolipoproteins were determined by electroimmuno assay. Grundy SM, Am J Cardiol 1998;81:18B-25B. Plasma triglycerides and cholesterol were determined enzymatically. Auerbach BJ, et al., J Lipid Res 1995;36:2541-51. Plasma lipoprotein cholesterol distributions were determined by high-performance gel-filtration chromatography with post-column detection. Kieft KA, et al., J Lipid Res 1991;32:859-66.

[00167] Results

[00168] With regard to plasma lipid and lipoprotein changes, Figures 1A (Genetic Models) and 1B (Charles River Laboratories) show the increase in plasma total cholesterol levels, over the 32 day sampling period. Figures 2A (Genetic Models) and 2B (Charles River Laboratories) show the decrease in plasma triglycerides levels, over the 32 day sampling period. Figures 3A (Genetic Models) and 3B (Charles River Laboratories) show the changes in plasma non-HDL-cholesterol levels, over the 32 day sampling period. Figures 4A (Genetic Models) and 4B (Charles River Laboratories) show the increase in plasma HDL-cholesterol levels over the 32 day sampling period. Figures 5A (Genetic Models) and 5B (Charles River Laboratories) show the increased ratio of plasma HDL-C to plasma non-HDL-C over the 32 day sampling period.

[00169] Plasma levels of select apolipoproteins were evaluated at the end of 32 day treatment and compared to the levels in the control treated animals. Figures 6A (Genetic Models) and 6B (Charles River Laboratories) show the changes in plasma apolipoprotein A-I, E, C-II and C-III on the 32nd day of sampling.

[00170] Plasma levels of markers of glycemic control were also determined. Figures 7A (Genetic Models) and 7B (Charles River Laboratories) show the changes in blood glucose levels over the 32 day sampling period. Figures 8A (Genetic Models) and 8B (Charles River Laboratories) show the changes in plasma insulin levels over the 32 day sampling period. Figures 9A (Genetic Models) and 9B (Charles River Laboratories) show the ratio of blood glucose levels/insulin levels on day 32nd day of sampling. These results show an improved glucose to insulin ratio, suggesting the Zucker rats are more insulin sensitive given gemcabene. That is, given gemcabene, less plasma insulin was needed to maintain glucose levels compared to the control rats receiving placebo. Interestingly, the rats receiving gemcabene did show an improved glucose tolerance test. Therefore, due to these contradicatory findings, it was unclear whether or not gemcabene could improve insulin sensitivity in a human. In this regard, an evaluation was conducted on the insulin sensitivity of gemcabene in a human clinical trial using the euglycemic hyperinsulinemic clamp method (Example 2, with results shown in Table 8 and Figure 13D).

[00171] Figures 10A (Genetic Models) and 10B (Charles River Laboratories) show the changes in body weight over the 32 day sampling period. Figures 11A (Genetic Models) and 11B (Charles River Laboratories) show the changes in liver weight on day 32nd day of sampling. Figures 12A (Genetic Models) and 12B (Charles River Laboratories) show the percent liver weight to body weight on day 32nd day of sampling.

[00172] The data was also analyzed to reflect the numbers ± SEM. Gemcabene caused a significant increase in HDL cholesterol in both models at all dose levels (Table 1). The HDL levels increased greater than 10-fold above the control values at both the 30- and 100-mg/kg dose. While there was very little effect on VLDL and LDL cholesterol (Table 2), the HDL-C/(VLDL-C+LDL-C) ratio was greatly improved (Table 2). Plasma triglycerides were significantly lowered by greater than 75% in both models (Table 3). Apo E plasma concentrations were increased 4- and 8-fold in Zuckers from Charles River and Genetic Models, respectively. Plasma apo-CII plasma concentrations were decreased at all dose levels in rats from both sources. The effect on plasma apo-CIII concentrations varied by dose and source (Table 4). Gemcabene produced a small decrease in blood glucose levels at the highest dose and a significant decrease in plasma insulin levels (Table 5). An improvement in glucose tolerance was not found. Gemcabene treatment resulted in a 2-fold increase in liver weight at all dose levels (Table 6). Additionally, there was an approximate 10% decrease in total body weight at the 30- and 100-mg/kg dose of gemcabene.

TABLES

TABLE 1. Effects of CI-1027 on Plasma Total and HDL Cholesterol in Female Obese Zucker Rats From 2 Sources

Treatment Group	Dose (mg/kg)	Total Cholesterol (mg/dL)				HDL Cholesterol (mg/dL)			
		Day 0	Day 7	Day 21	Day 32	Day 0	Day 7	Day 21	Day 32
Genetic Models									
Control		114 ± 8	107 ± 10	120 ± 9	98 ± 12	49 ± 6	36 ± 3	30 ± 4	24 ± 3
CI-1027	30	97 ± 4	264 ± 16[c]	350 ± 30[c]	412 ± 38[c]	50 ± 5	232 ± 13[c]	272 ± 30[c]	324 ± 33[c]
	100	102 ± 7	340 ± 12[c]	450 ± 32[c]	384 ± 61[c]	43 ± 2	278 ± 10[c]	363 ± 18[c]	330 ± 42[c]
Charles River									
Control		118 ± 9	109 ± 14	96 ± 6	76 ± 5	62 ± 12	46 ± 3	52 ± 8	35 ± 6
CI-1027	10	111 ± 11	218 ± 30[b]	281 ± 51[b]	265 ± 38[c]	73 ± 6	178 ± 24[c]	243 ± 50[b]	232 ± 26[c]
	30	137 ± 8	390 ± 22[c]	681 ± 56[c]	555 ± 14[c]	76 ± 7	345 ± 36[c]	602 ± 46[c]	504 ± 12[c]
	100	125 ± 8	316 ± 37[c]	320 ± 38[c]	413 ± 29[c]	65 ± 7	269 ± 28[c]	282 ± 38[c]	390 ± 28[c]

Data are mean ± SEM (n = 6 rats/group).
Data were analyzed by 2-sided unpaired t-tests.
[a] Significantly different than respective control (<0.01)
[b] Significantly different than respective control (<0.05)
[c] Significantly different than respective control (<0.001)

TABLE 2. Effects of CI-1027 on Plasma VLDL + LDL Cholesterol and HDL/(VLDL-C + LDL-C) Ratio in Female Zucker Rats From 2 Sources

Treatment Group	Dose (mg/kg)	VLDL + LDL Cholesterol (mg/dL)				HDL-C/(VLDL-C + LDL-C)			
		Day 0	Day 7	Day 21	Day 32	Day 0	Day 7	Day 21	Day 32
Genetic Models									
Control		83 ± 13	81 ± 12	107 ± 15	82 ± 11	0.72 ± 0.17	0.47 ± 0.05	0.33 ± 0.08	0.30 ± 0.04
CI-1027	30	63 ± 3	32 ± 4[a]	82 ± 10	89 ± 9	0.80 ± 0.06	7.82 ± 0.98[a]	3.72 ± 0.71[b]	3.72 ± 0.34[c]
	100	73 ± 11	60 ± 9	87 ± 18	53 ± 19	0.63 ± 0.09	3.06 ± 0.65[c]	3.03 ± 0.81[c]	7.81 ± 0.93[c]
Charles River									
Control		65 ± 12	71 ± 16	50 ± 9	46 ± 9	1.27 ± 0.40	0.92 ± 0.27	1.25 ± 0.29	1.03 ± 0.30
CI-1027	10	52 ± 10	38 ± 7	36 ± 2	32 ± 5	1.59 ± 0.25	4.88 ± 0.55[c]	6.68 ± 1.18[b]	7.93 ± 1.12[c]
	30	65 ± 12	43 ± 3	77 ± 13	48 ± 12	1.48 ±0 .39	8.15 ± 0.52[c]	8.48 ± 0.90[c]	11.01 ± 1.03[c]
	100	68 ± 12	46 ± 16	38 ± 5	20 ± 3[b]	1.16 ± 0.28	8.19 ± 1.62[b]	8.92 ± 2.21[b]	20.05 ± 1.69[c]

Data are mean ± SEM (n = 6 rats/group).

Data were analyzed by 2-sided unpaired t-tests.

[a] Significantly different than respective control (<0.01)

[b] Significantly different than respective control (<0.05)

[c] Significantly different than respective control (<0.001)

TABLE 3. Effects of CI-1027 on Plasma Triglycerides in Female Obese Zucker Rats From 2 Sources

Treatment Group	Dose (mg/kg)	Triglycerides (mg/dL)			
		Day 0	Day 7	Day 21	Day 32
Genetic Models					
Control		1038 ± 143	1209 ± 264	1600 ± 100	1201 ± 162
CI-1027	30	857 ± 66	237 ± 29[b]	837 ± 132[c]	743 ± 63[b]
	100	988 ± 155	367 ± 41[a]	563 ± 128[c]	257 ± 92[c]
Charles River					
Control		920 ± 136	882 ± 163	791 ± 146	749 ± 161
CI-1027	10	964 ± 178	271 ± 32[b]	319 ± 38[a]	270 ± 53[a]
	30	847 ± 154	242 ± 19[b]	415 ± 72[a]	331 ± 61[a]
	100	967 ± 170	264 ± 78[b]	179 ± 29[b]	87 ± 12[b]

Data are mean ± SEM (n = 6 rats/group).
Data were analyzed by 2-sided unpaired t-tests.
[a] Significantly different than respective control (<0.01)
[b] Significantly different than respective control (<0.05)
[c] Significantly different than respective control (<0.001)

TABLE 4. Effects of CI-1027 Plasma Apolipoproteins in Female Zucker Rats From 2 Sources

Treatment Group	Dose (mg/kg)	Percent of Control[a]			
		Apo-AI	ApoE	ApoC-II	ApoC-III
Genetic Models					
Control		100 ± 8	100 ± 5	100 ± 6	100 ± 10
CI-1027	30	115 ± 6	803 ± 40[c]	45 ± 7[c]	131 ± 8[a]
	100	88 ± 10	880 ± 64[c]	9 ± 1[c]	55 ± 13[a]
Charles River					
Control		100 ± 3	100 ± 7	100 ± 10	100 ± 13
CI-1027	10	85 ± 3[b]	269 ± 19[c]	41 ± 5[c]	134 ± 22
	30	103 ± 4	414 ± 10[c]	34 ± 4[c]	287 ± 30[c]
	100	96 ± 5	357 ± 12[c]	12 ± 1[c]	88 ± 10

Data are mean ± SEM (n = 6 rats/group).
Data were analyzed by 2-sided unpaired t-tests.
[a] Significantly different than respective control (<0.01)
[b] Significantly different than respective control (<0.05)
[c] Significantly different than respective control (<0.001)

TABLE 5. Effects of CI-1027 on Blood Glucose and Insulin in Obese Female Zucker Rats From 2 Sources

Treatment Group	Dose mg/kg	Blood Glucose (mg/dL)						Plasma Insulin (ng/mL)	Glucose/ Insulin
		Day 0	Day 7	Day 14	Day 21	Day 28	Day 32	Day 32	
Genetic Models									
Control		109 ± 6	106 ± 5	96 ± 4	111 ± 7	96 ± 6	99 ± 9	22.6 ± 3.1	47.3 ± 6
CI-1027	30	117 ± 8	94 ± 4	92 ± 14	132 ± 31	180 ± 55	198 ± 59	7.8 ± 1.5[b]	325 ± 136
	100	104 ± 6	86.3 ± 3[b]	71 ± 5[b]	75 ± 4[c]	87 ± 4	84 ± 8	2.8 ± 1.2[c]	494 ± 112[b]
Charles River									
Control		100 ± 4	91 ± 3	93 ± 5	85 ± 5	93 ± 2	80 ± 1	3.1 ± 0.38	299 ± 67
CI-1027	10	108 ± 7	100 ± 10	94 ± 4	97 ± 4	105 ± 5[a]	94 ± 6[a]	1.49 ± 0.22[b]	682 ± 86[b]
	30	102 ± 9	93 ± 3	92 ± 10	91 ± 5	91 ± 5	101 ± 4[a]	1.57 ± 0.21[b]	685 ± 67[b]
	100	100 ± 5	84 ± 7	76 ± 3[a]	68 ± 5[b]	74 ± 3[c]	85 ± 4	1.08 ± 0.13[c]	846 ± 98[c]

Data are mean ± SEM (n = 6 rats/group).

Data were analyzed by 2-sided unpaired t-tests.

[a] Significantly different than respective control (<0.01)

[b] Significantly different than respective control (<0.05)

[c] Significantly different than respective control (<0.001)

TABLE 6. Effects of CI-1027 on Body Weight and Liver Weight in 2 Models of Female Obese Zucker Rats

Treatment Group	Dose mg/kg	Body Weight (gm)						Liver Weight (gm)	Percent Liver/Body Weight
		Day 0	Day 7	Day 14	Day 21	Day 28	Day 32	Day 32	
Genetic Models									
Control		268 ± 4	299 ± 4	328 ± 4	350 ± 6	370 ± 5	379 ± 6	14.0 ± 0.4	3.70 ± 0.1
CI-1027	30	265 ± 4	283 ± 4[c]	299 ± 4[c]	311 ± 3[c]	317 ± 4[c]	321 ± 4[c]	22.8 ± 1.0[c]	7.09 ± 0.3[c]
	100	265 ± 4	286 ± 3[c]	302 ± 4[b]	314 ± 4[c]	326 ± 5[c]	329 ± 5[c]	24.8 ± 1.3[c]	7.53 ± 0.3[c]
Charles River									
Control		306 ± 9	338 ± 7	362 ± 9	377 ± 11	398 ± 11	409 ± 10	12.1 ± 0.3	2.97 ± 0.1
CI-1027	10	305 ± 12	332 ± 10	352 ± 10	361 ± 6	382 ± 7	387 ± 6	22.2 ± 1.3[c]	5.73 ± 0.3[c]
	30	324 ± 6	346 ± 7	358 ± 9	377 ± 10	395 ± 10	402 ± 11	26.3 ± 1.4[c]	6.52 ± 0.2[c]
	100	287 ± 6	305 ± 5[b]	314 ± 4[c]	329 ± 4[b]	351 ± 4[b]	363 ± 4[b]	23.8 ± 0.7[c]	6.55 ± 0.1[c]

Data are mean ± SEM (n = 6 rats/group).

Data were analyzed by 2-sided unpaired t-tests.

[a] Significantly different than respective control (<0.01)

[b] Significantly different than respective control (<0.05)

[c] Significantly different than respective control (<0.001)

[00173] Gemcabene beneficially modified the lipoprotein profile in these models of NIDDM. The insulin sensitizing effect of gemcabene was also evident in both Zucker rat models, but there was no change in the glucose tolerance. The above studies are carried out in rats and do not directly provide evidence of the behavior of gemcabene in humans. To further investigate these observations, we assessed effect of gemcabene on average glucose disposal rate (GDR) during the last 30 minutes of a 3-hour euglycemic hyperinsulinemic clamp in healthy, obese, non-diabetic human subjects prior to and after 4 weeks once daily with 900 mg gemcabene or once daily placebo.

[00174] **Example 2**

[00175] Clinical Design-Improved insulin sensitization in human obese non-diabetic subjects.

[00176] To determine the effects of gemcabene on insulin sensitivity, a euglycemic hyperinsulinemic clamp study was performed. The euglycemic hyperinsulinemic clamp, also known as a hyperinsulinemic clamp, requires acutely raising the insulin level by a continuous infusion of insulin. Meanwhile, the plasma glucose concentration is held constant at basal levels by a variable glucose infusion. When the steady-state is achieved, the glucose infusion rate equals glucose uptake by all the tissues in the body and is therefore a measure of tissue insulin sensitivity.

[00177] Subjects were enrolled in a double-blind, placebo-controlled, multiple-dose, multicenter study. Subjects of any race and either gender were required to meet the following criteria in order to be eligible to participate in the study: age ≥18 years; body mass index between 30 and 40 kg/m2; fasting glucose <126 mg/dL; and be in good health. Fifty-three subjects (37 male, 16 female) ranging in age from 26 to 63 years entered the study and were randomized to receive either 900 mg gemcabene or placebo once daily on Day 2 through Week 4. A hyperinsulinemic clamp study was performed on Day 1 and one hour following the last dose of gemcabene at the end of the fourth week of treatment. Fifty subjects completed the study.

Table 7

Baseline Characteristics	Gemcabene	Placebo
N	24	26
Mean Age in years	44.5	43.9
Sex – Male (%)	17 (81%)	17 (65%)
Race – Caucasian (%)	20 (83%)	19 (73%)
TC (mg/dL)	198.4	182.5
LDL-C (mg/dL)	119.1	106.3
TG (mg/dL)	171.4	161.8
Fasting glucose (mg/dL)	97.5	102.3

[00178] The criteria for evaluation were efficacy, pharmacokinetic/pharmacodynamics, and safety. The primary efficacy measure was insulin sensitivity as defined by average glucose disposal rate during the last 30 minutes of a 3-hour euglycemic hyperinsulinemic clamp study.

[00179] Insulin sensitivity was measured with the 3-hour euglycemic hyperinsulinemic clamp technique. Before each clamp study, subjects are required to fast for 10 to 12 hours overnight. A polyethylene cannula was inserted into an antecubital vein for the infusion of test substances. A second catheter was inserted retrogradely into an ipsilateral wrist vein on the dorsum of the hand for blood sampling and the hand kept in a heated box at 65°C.

[00180] After the basal equilibration period, insulin is administered as a primed continuous infusion at the rate of 40 mU/m^2/minute for 180 minutes. The plasma glucose concentration was measured every five minutes after the start of the insulin infusion, and a variable infusion of 20% glucose was adjusted based on the negative feedback principle to maintain the plasma glucose level at 90 mg/dL. Plasma samples were collected every 15 minutes from 0 to 150 minutes and every 5 to 10 minutes from 150 to 180 minutes for determination of plasma glucose.

[00181] **Statistical Methods**

[00182] The percent change from baseline in the glucose disposal rate was compared for the placebo and active groups using a 2-sample t-test. The 95% lower confidence bound on the mean effect of gemcabene minus placebo, and the 1-sided p-value for H0: Mean treatment difference =0 are reported.

[00183] **Pharmacokinetic/Pharmacodynamics**

[00184] Measureable plasma concentrations were present in all samples assayed. Based on the 49 samples assayed, the mean (±SD) plasma gemcabene concentration was 136.6 (±56.3) µg/mL. This was in the expected range as trough plasma concentrations in a multiple dose tolerance study following 900 mg gemcabene capsules ranged from 117 to 146 µg/mL.

[00185] **Safety results**

[00186] Multiple doses of gemcabene (900 mg once daily in the morning [QAM] for 4 weeks) were generally well-tolerated. There were no deaths, serious adverse events, or withdrawals due to adverse events, during the study. There were no clinically significant changes in physical examinations, vital signs, ECGs or laboratory measurements.

[00187] **Results**

[00188] Gemcabene was generally well-tolerated and associated with a 6.76% mean increase in glucose disposal rate compared to placebo as shown in Table 8.

Table 8

Inferential Statistics on the Percent Change from Baseline in the Glucose Disposal Rate.

Gemcabene Mean % Change	Placebo Mean % Change	Gemcabene – Placebo			95% Lower Confidence Bound	One-Sided p-value For H_0: Mean = 0
		Mean	SE	df		
13.11	6.35	6.76	8.17	48	-6.94	0.2059
SE = Standard error; df = Degrees of freedom for the difference between gemcabene and placebo						

[00189] The data show a trend for improved insulin sensitization in obese non-diabetic subjects administered in a euglycemic clamp study. In order to maintain euglycemia, about twice the amount of glucose was needed to be infused in the group given gemcabene compared with the placebo treated group. Multiple doses of gemcabene were generally well-tolerated. Treatment with gemcabene was associated with a mean increase in the percent change from baseline in the glucose disposal rate, but the comparison to placebo did not attain statistical significance.

[00190] Using the paired-t-test in a post-hoc analysis, gemcabene lowered mean total cholesterol (TC), LDL-C and triglycerides (TGs) by 27% ($p < 0.0001$), 40% ($p < 0.0001$), and 3.2% (NS), respectively and gemcabene increased mean glucose disposal rate by 13% ($p < 0.0178$). (Figures 13A, 13B, 13C, 13D) Figures 13A-13D also show the percent changes from

pretreatment levels for cholesterol (13A), LDL-C (13B), triglycerides (13C) and mean glucose disposal rate (13D).

[00191] Example 3

[00192] Clinical Design (GEM301)

[00193] This was a Phase 2, randomized, placebo-controled, double blind, multicenter study.

[00194] A wash-out period was required for eligible subjects taking any lipid-regulating therapies or supplements, with the exception of atorvastatin (10, 20, 40, or 80 mg QD), rosuvastatin (5, 10, 20, or 40 mg QD), simvastatin (20 or 40 mg QD), or ezetimibe 10 mg QD. For subjects who required a wash-out period, the Pre-Screening Visit was their first study visit and occurred prior to the Screening Visit based on the duration of the wash-out period required. The duration of the wash-out period was dependent upon the status of the subject's current lipid-regulating therapy. Specifically, PCSK9 inhibitors required an 8-week wash-out period, fibrates required a 6-week wash-out period, and niacin or other lipid-regulating therapies such as bile acid sequestrants required a 4-week wash-out period prior to the Screening Visit.

[00195] All eligible subjects participated in the Screening Visit up to 14 days prior to Day 1. For eligible subjects taking the required stable statin therapy for $\geq$ 12 weeks and who did not require a wash-out period, the Screening Visit was their first study visit.

[00196] As shown in Table 9, subjects were required to be on either a high-intensity stable statin reginmen (atorvastatin 40 or 80 mg QD; or rosuvastatin 20 or 40 mg QD) or a moderalte-intensity statin regimen (atorvastatin 10 or 20 mg QD; rosuvastatin 5 or 10 mg QD; or simvastatin 20 or 40 mg QD) with or without ezetimibe 10 mg QD for at least 12 weeks prior to the Screening Visit.

Table 9

High-intensity vs Moderate-intensity Classifications	
High-intensity Dosage (QD)	Moderate-intensity Dosage (QD)
Atorvastatin 40 mg, 80 mg Rosuvastatin 20 mg, 40 mg	Atorvastatin 10 mg, 20 mg Rosuvastatin 5 mg, 10 mg Simvastatin 20 mg, 40 mg

[00197] Subjects were randomized on Day 1 in a 1:1 ratio to the following treatment groups placebo or gemcabene 600 mg. Subjects were stratified by statin intensity (high-intensity dosage; moderate-intensity dosage) and Type 2 diabetes (yes or no). The first dose of study drug was administered at the site on Day 1. On days with a scheduled office visit with blood

sample collection, subjects remained fasted (at least 10 hours) and should not have taken gemcabene until after the blood samples were collected. For days when the subject self-dosed, subjects were instructed to take study drug at the same time in the morning with a full glass (8 ounces) of water either with or without food.

[00198] This was a double-blind study; the sponsor and all clinical site personnel (investigator, pharmacist, etc.) were blinded to the treatment group for each subject. Subjects also were blinded to the treatment they received.

[00199] Post-randomization clinic visits occurred at Week 2, Week 4, Week 8, and Week 12. The Follow-up Visit occurred 4 weeks (±3 days) after the last dose of study drug.

[00200] Prior gemcabene dose response analysis on LDL-C in individual studies, as well as across Phase 2 studies, indicate gemcabene 600 mg is the optimal dose to move forward for testing in Phase 3. What is not known is the ability of gemcabene at its optimal dose (600 mg) to provide clinically and statistically meaningful LDL-C lowering in subjects not at goal (LDL-C >100 mg/dL) while receiving maximum statin therapy, including high-intensity statin and moderate-intensity statin therapy. Therefore, the current study was designed to assess the effect of gemcabene 600 mg on LDL-C and other lipids and hsCRP in subjects whose LDL-C > 100 mg while on stable statin therapy, of which 50% was high-intensity and 50% was moderate-intensity.

[00201] Demographic and Baseline Characteristics

[00202] Demographic information was summarized using descriptive statistics by randomized treatment group and overall for the FAS. Additionally, demographic information was presented by statin-intensity stratum (moderate and high), for diabetic subjects, and for subjects with and without mixed dyslipidemia. Explicitly, the following characteristics were summarized: 1) sex (male, female); 2) menopausal status for females, 3) race, 4) ethnicity; 5) age; 6) height; 7) weight; 8) and BMI.

[00203] Age was computed for each subject using the following formula:

Age = integer ([Screening Visit date – date of birth]/365.25).

[00204] BMI was calculated using the following formula:

BMI = (body weight in kilograms)/(height in meters)^2.

[00205] Primary Efficacy Endpoint Analysis Methods

[00206] The primary efficacy endpoint (percent change from baseline to Week 12 in LDL-C) was analyzed using analysis of covariance (ANCOVA) and the full analysis set (FAS) population. The null hypothesis tested was that there was no difference in the expected percent change from baseline to Week 12 in LDL-C between the active treatment (subjects treated with

gemcabene 600 mg) and placebo (subjects treated with placebo) groups after adjusting for baseline statin-intensity stratum, baseline diabetes status, and baseline LDL-C. Explicitly, in the ANCOVA, percent change from baseline to Week 12 in LDL-C was the dependent variable whereas randomized treatment group (gemcabene 600 mg or placebo), baseline statin-intensity stratum (moderate or high), and baseline diabetes status (yes or no) were included as factors, and baseline LDL-C was included as a covariate. Baseline was defined as the average of the LDL-C values at Screening/Visit S1 and pre-dose Day 1/Visit T1. Last observation carried forward was used to impute missing values for Week 12; only post-baseline values were used for imputation. The least-squares mean (LSM) and standard error for percent change from baseline to Week 12 in LDL-C for each treatment group and the LSM and 95% confidence interval (CI) of the treatment difference were produced from the model using type III sums of squares to estimate the magnitude of the treatment effect.

[00207] Secondary and Other Efficacy Endpoint Analysis Methods

[00208] All secondary analyses were conducted using the FAS population (or the specific subgroup within the FAS population, eg, diabetic subjects both predetermined and actual) with subjects included in their randomized treatment group regardless of the treatment they actually received.

[00209] Similar analysis of ANCOVA as specified for the primary analysis in the above section was conducted for the secondary efficacy endpoints. Note the covariate included in the ANCOVA was the baseline value of the parameter of interest (eg, if the parameter of interest was HDL-C, the covariate in the ANCOVA was HDL-C at baseline). In addition, for secondary endpoints such as change from baseline in LDL-C within the moderate-intensity stratum, the ANCOVA model did not include a term for baseline statin-intensity stratum.

[00210] Baseline for TC, non-HDL-C, HDL-C and VLDL-C were defined similarly to baseline for LDL-C. Baseline for fasting lipoproteins, hsCRP, serum Amyloid A (SAA), fibrinogen, adiponectin, fasting plasma glucose (FPG), fasting insulin, and serum PCSK9 were defined as the value from pre-dose Day 1/Visit T1. Baseline for HbA1c was the value from the first visit (Pre-Screening or Screening Visit).

[00211] Because hsCRP and TC were non-normally distributed, these parameters were analyzed using ranked ANCOVA. Results of parametric ANCOVA were also provided for these parameters as supportive results. Ranked ANCOVA was conducted by first ranking the outcome and covariate at a given time point (eg, Week 12) prior to conducting ANCOVA. The P-value corresponding to the difference in ranked outcome between treatment groups was the output, and results were interpreted in the context of the median change from baseline for each

treatment group. Only the ranked ANCOVA results are presented for parameters not normally distributed.

[00212] The secondary efficacy endpoints that were binary were analyzed using logistic regression. The logistic regression model included the indicator for meeting the criteria (eg, achieving a LDL-C reduction from baseline of ≥ 10% at Week 12) as the dependent variable; and randomized treatment group, baseline statin-intensity stratum, baseline diabetes status, and baseline LDL-C as independent factors. The output from each logistic regression model included the odds ratio (OR), 95% CI, and the associated P-value.

[00213] GEM-301 was designed to determine the safety and additional LDL-C lowering of gemcabene 600 mg over 12 weeks in 105 subjects with LDL-C ≥ 100 mg/dL and TG < 500 mg/dL while on high and moderate-intensity stable background statin therapy +/- ezetimibe. A total of 105 subjects were randomized (55 subjects [52.4%] and 50 subjects [47.6%] in the moderate-intensity and high-intensity statin stratums, respectively) with a median age of 63.0 years, the majority female (53.3%) and white (77.1%), a mean BMI of 30.6 kg/m2, and a mean baseline LDL-C of 130.2 mg/dL. Gemcabene 600 mg demonstrated a statistically significant mean percent change from baseline when compared with placebo (-16.0% vs -5.0%, p = 0.0057) at Week 12. Consistent with the mechanism of action of gemcabene, decreased atherogenic burden was observed with mirrored statistically significant lowering to LDL-C in non-HDL-C, ApoB, and ApoE. Note that in the human, apoE decreases in the plasma, and is unlike the observation in the rat, where apoE in the plasma is markedly increased with gemcabene treatment. In the rat , apoE is predominantly carried on HDL (which are markedly elevated given gemcabene), while in the humans, apoE is predominantly carried on VLDL and VLDL remnants (whose clearance along with apoE is enhanced given gemcabene).

[00214] **Example 4**

[00215] A post-hoc subpopulation analysis was conducted whereby the study population was segregated into two groups, subjects with BMI below 30 and subjects with BMI equal to or greater than 30. The subject data was evaluated for select lipids, lipoproteins, apolipoprotein B, and high sensitivity C-reative protein, (hs-CRP) an indication of inflammation.

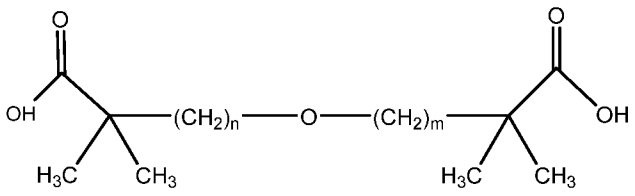
[00216] In subjects with BMI ≥ 30, a greater percent reduction from baseline was observed for LDL-C , triglycerides, apolipoprotein B, non-HDL-cholesterol and hs-CRP than for subjects having a BMI <30 (Table 10).

Table 10

		LDL Mean	TRIG Mean	APOB Mean	NONHDL Mean	HSCRP Median
		Gemcabene 600mg	Gemcabene 600mg	Gemcabene 600mg	Gemcabene 600mg	Gemcabene 600mg
BMI < 30	N	31	31	31	31	30
	Baseline	138	130	109	164	1.3
	Final	117	117	95	141	1.0
	% Change Baseline	-15.7	-5.4	-12.7	-14.2	-34.5
	Change Baseline	-21.3	-13.0	-14.5	-23.8	-0.3
BMI ≥ 30	N	23	23	23	23	22
	Baseline	131	156	108	162	3.0
	Final	106	138	91	134	1.5
	% Change Baseline	-19.0	-11.1	-14.8	-17.3	-42.3
	Change Baseline	-24.5	-18.3	-17.1	-28.3	-1.3

What is claimed is:

1. A method for treating lipodystrophy, comprising administering to a patient in need therof a compound of formula II, wherein the compound of formula II is

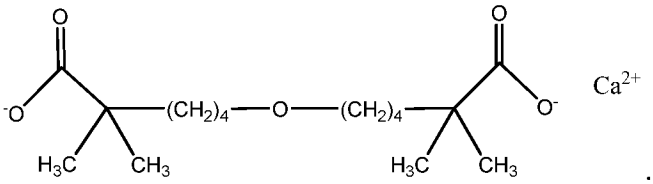


(II)

or an ester, or a hydrate, or salt thereof,

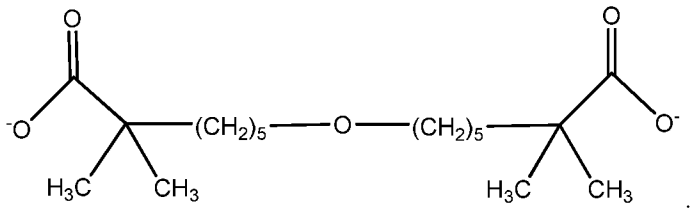
wherein n, m independently are integers from 2 to 9.

2. The method of claim 1, wherein the compound of formula II is



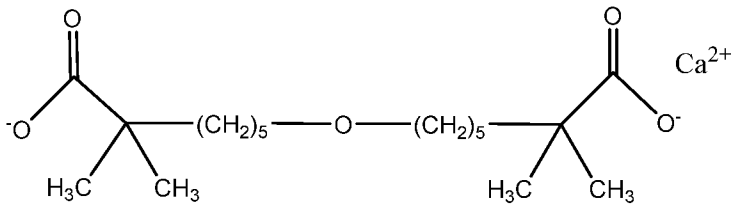
.

3. The method of claim 1, wherein the compound of formula II is



.

4. The method of claim 1, wherein the compound of formula II is



.

5. The method of any one of claims 1-4, wherein the lipodystropy is a familial partial lipodystrophy (FPL).

6. The method of any one of claims 1-5, wherein the compound of formula II is administered with an additional agent.

7. The method of claim 6, wherein the additional agent is leptin, a leptin analog, a leptin derivative, insulin, a fibrate, a thiazolidinedione, niacin, a niacin derivative, Eicosapentenoic

acid (20:5), an ester of Eicosapentenoic acid, a prodrug of Eicosapentanoic acid, metformin, a statin, an oral hypoglycemic agent, an injectable hypoglycemic agent, an apo C-III antisense molecule, an apoC-III DNAi, an apoC-III siRNA, fish oil, a PCSK9 inhibitor, a cholesterol absorption inhibitor, a bile acid sequestrant, an appetite suppressing agent, or an anti-hypertensive agent.

8. The method of claim 7, wherein the fibrate is gemfibrozil, fenofibric acid, bezafibrate, or clofibrate.

9. The method of claim 7, wherein the thiazolidinedione is rosiglitazone or pioglitazone.

10. The method of claim 7, wherein the statin is atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or pitavastatin.

11. The method of claim 7, wherein the cholesterol absorption inhibitor is ezetimibe.

12. The method of claim 7, wherein the leptin analog is metreleptin.

13. The method of claim 7, wherein the anti-hypertensive agent is a calcium channel blocker, an ACE inhibitor, a beta-blocker, an angiotensin II receptor blocker, an alpha-2 receptor agonist, a vasodilator or a diuretic.

14. The method of claim 7, wherein the additional agent is an oral hypoglycemic agent and the oral agent is a biguanide , a sulfonylurea, a thiazolidinedione, a meglitimide, a D-phenylalanine derivative, an alpha-glucosidase inhibitor, a bile acid sequestrant, an insulin secretagogue, a DPP-4 inhibitor, or a combination thereof.

15. The method of claim 7, wherein the additional agent is an injectable hypoglycemic agent and the injectable hypoglycemic agent is leptin, a leptin analogue, a leptin derivative, insulin, an insulin analog, an insulin derivative, amylin, a synthetic amylin, an amylin analogue, a glucagon-like peptide-1 (GLP-1), a GLP-1 analog, or a GLP-1 derivative, or a combination thereof.

16. The method of claim 7, wherein the amylin analogue is pramlintide or exenatide.

17. The method of claim 1-16, wherein the insulin sensitivity of the patient is increased.

18. The method of any one of claims 1-17, wherein the patient requires less insulin to maintain glycemic control after administration of the compound of formula II when compared with the amount of insulin required prior to administration of the compound of formula II.

19. A method of administering a compound of formula II for treatment of medical complications of FPL wherein the method results in:

a) lowering the level of plasma apoC-III in a patient with FPL;

b) lowering the level of plasma triglyceride in a patient with FPL;

c) preventing pancreatitis in a patient with FPL;

d) reducing the incidence of pancreatitis in a patient with FPL;

e) lowering plasma VLDL-C in a patient with FPL;

f) lowering plasma LDL-C in a patient with FPL;

g) elevating plasma HDL-C in a patient with FPL;

h) lowering inflammation in a patient with FPL; or

i) lowering pain in a patient with FPL.

20. A method of administering a compound of formula II for treating, reducing, and preventing of medical complications in a patient with FPL comprising administering a compound of formula II or an ester, or a hydrate, or a salt thereof, wherein the administering results in treating, reducing, or preventing

a) a cardiovascular disease in a patient with FPL;

b) an inflammatory conditions or disease;

c) an abnormal redistribution of body fat in a patient with FPL;

d) body weight gain in a patient with FPL;

e) acanthosis nigricans in a patient with FPL;

f) hyperphagia in a patient with FPL;

g) neuropathy in a patient with FPL;

h) kidney disease in a patient with FPL;

i) complcations of vision or the eye;

j) hypertension;

k) foot complications; or

l) amputation.

21. A method of administering a compound of formula II or an ester, or a hydrate, or a salt thereof for delaying the time of onset or the severity of symptoms of FPL in a patient with FPL.

22. The method of any one of claim 1-21, wherein the compound of formula II or an ester, or a hydrate, or a salt thereof is administered with an additional agent.

23. The method of claim 22, wherein the additional agent is leptin, a leptin analog, a leptin derivative, insulin, a fibrate, a thiazolidinedione, niacin, a niacin derivative, Eicosapentenoic acid (20:5), an ester of Eicosapentenoic acid, a prodrug of Eicosapentenoic acid, metformin, a statin, an oral hypoglycemic agent, an injectable hypoglycemic agent, an apo C-III antisense molecule, an apoC-III DNAi, an apoC-III siRNA, fish oil, a PCSK9 inhibitor, a cholesterol absorption inhibitor, a bile acid sequestrant, an appetite suppressing agent, or an anti-hypertensive agent.

24. The method of claim 23, wherein the

a) fibrate is gemfibrozil, fenofibric acid, bezafibrate, or clofibrate;

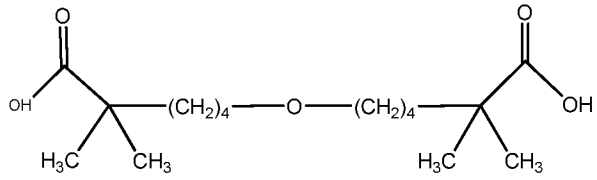
b) thiazolidinedione is rosiglitazone or pioglitazone;

c) statin is atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or pitavastatin;

d) cholesterol absorption inhibitor is ezetimibe; or

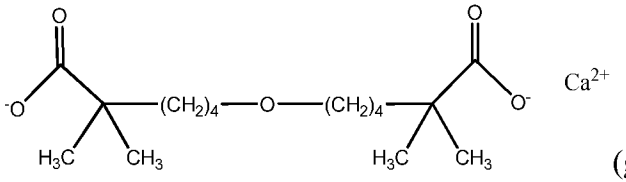
e) leptin analog is metreleptin.

25. The method of any one of claims 1 or 5-24, wherein compound of formula II is 6,6'-oxybis-(2,2'-dimethylhexanoic acid) also referred to herein in as gemcabene.



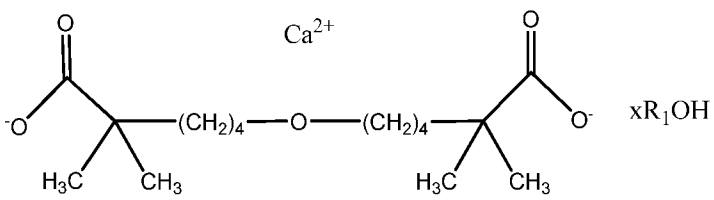
(gemcabene).

26. The method of any one of claims 1 or 5-24, wherein compound of formula II is the anhydrous monocalcium salt of gemcabene (gemcabene calcium):



(gemcabene calcium).

27. The method of any one of claims 1 or 5-24, wherein compound of formula II is the hydrate of the monocalcium salt:



wherein x is an integer from 1 to 10.

28. The method according to any one of claims 1-27, wherein the patient has one or more residual risk factors, including elevated plasma triglycerides, high sensitivity C-reactive protein, non-HDL cholesterol, apoC-II, apo C-III, fasting glucose, fasting insulin, or low plasma levels of HDL-C.

29. The method according to any one of claims 1-28, wherein the patient has elevated levels of LDL-C.

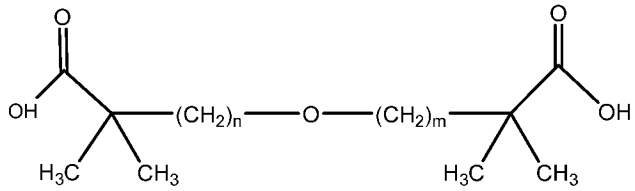
30. The method according to any one of claims 1-29, wherein compound is administered to the subject in a dose from about 25 mg to about 900 mg.

31. The method of claim 30, wherein the dose is 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, 450 mg, 600 mg, or 900 mg.

32. The method of claim 31, wherein the dose is 100 mg, 300 mg, 450 mg, 600 mg, or 900 mg.

33. The method according to any one of claims 30-32, wherein the dose is administered to the subject once daily.

34. A method comprising administering to the patient, in need thereof, an effective amount of a compound of formula (I):



(I)

or a salt, hydrate or alkyl ester thereof, wherein n and m are each independently the integer 3, 4, 5, or 6

a) for increasing insulin sensitivity in a patient in need thereof, the method;

b) for decreasing blood glucose levels;

c) for decreasing HbA1c levels; or

d) for increasing the glucose disposal rate,

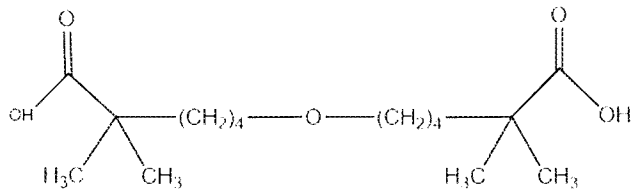
wherein the patient has a BMI ≥30.

35. The method according to claim 34, wherein m and n are the same integer.

36. The method according to claim 34, wherein m and n are different integers.

37. The method according to claim 34, wherein m and n are each 5.

38. The method according to claim 34, wherein the compound of formula (I) is



(gemcabene)

or a salt, or a hydrate thereof.

39. The method according to claim 38, wherein the compound is the calcium salt of gemcabene.

40. The method according to claim 38, wherein the compound is the monocalcium salt of gemcabene (gemcabene, calcium).

41. The method according to any one of claims 34-40, wherein compound is administered to the subject in a dose from about 25 mg to about 900 mg.

42. The method of claim 41, wherein the dose is 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, 450 mg, 600 mg, or 900 mg.

43. The method of claim 42, wherein the dose is 100 mg, 300 mg, 450 mg, 600 mg, or 900 mg.

44. The method according to any one of claims 41-43, wherein the dose is administered to the subject once daily.

45. The method according to any one of claims 34-44, wherein the patient is obese and not diabetic.

46. The method according to any one of claims34-45, wherein the patient is above normal body weight for height.

47. The method according to any one of claims 34-46, wherein the patient has impaired glucose tolerance.

48. The method according to any one of claims 34-46, wherein the glucose tolerance of the patient is improved.

49. The method according to any one of claims 34-48, wherein the patient has one or more residual risk factors, including elevated plasma triglycerides, high sensitivity C-reactive protein, non-HDL cholesterol, apoC-II, apo C-III, fasting glucose, fasting insulin, or low plasma levels of HDL-C.

50. The method according to any one of claims 34-49, wherein the patient has elevated levels of LDL-C.

51. The method according to any one of claims 34-50, wherein the compound is administered with an additional therapeutic agent.

52. The method of claim 51, wherein the additional agent is a glycemic control agent.

53. The method according to claim 52, wherein the glycemic control agent is administered orally.

54. The method according to claim 52, wherein the glycemic control agent is administered subcutaneously.

55. The method according to claim 52, wherein the glycemic control agent is administered intramuscularly.

56. The method according to claim 52, wherein the glycemic control agent is administered intravenously.

57. The method of claim 52, wherein the glycemic control agent comprises one of more of insulin, a modified insulin, a short acting insulin, a long acting insulin, a basal insulin, a bolus insulin, a glucagon-like protein 1 agonist, a meglitinide, a DPP-IV inhibitor, metformin, a sulfonylurea, an alpha-glucosidase inhibitor, a sodium glucose co-transporter 2 (SGLT2) inhibitor.

58. The method of claim 52, wherein the glycemic control agent is a thiazolidinedione.

59. The method according to any one of claims 34-58, wherein the insulin sensitivity is improved.

60. The method of claim 52, wherein the dose of the glycemic control agent administered to a patient in combination with a compound of Formula (1) is lower than the dose of the glycemic control agent is administered without the compound of Formula (1) to achieve a similar dynamic biological or glycemic control effect.

FIG. 1A

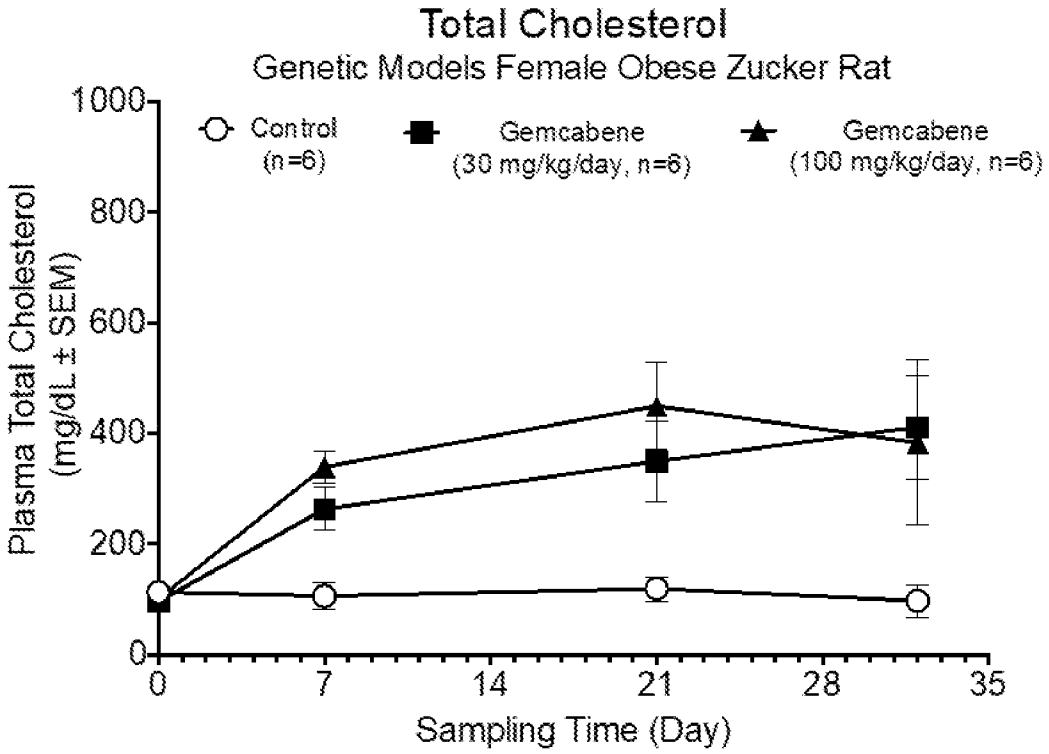

Total Cholesterol
Genetic Models Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma Total Cholesterol (mg/dL ± SEM)
1000
800
600
400
200
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 1B

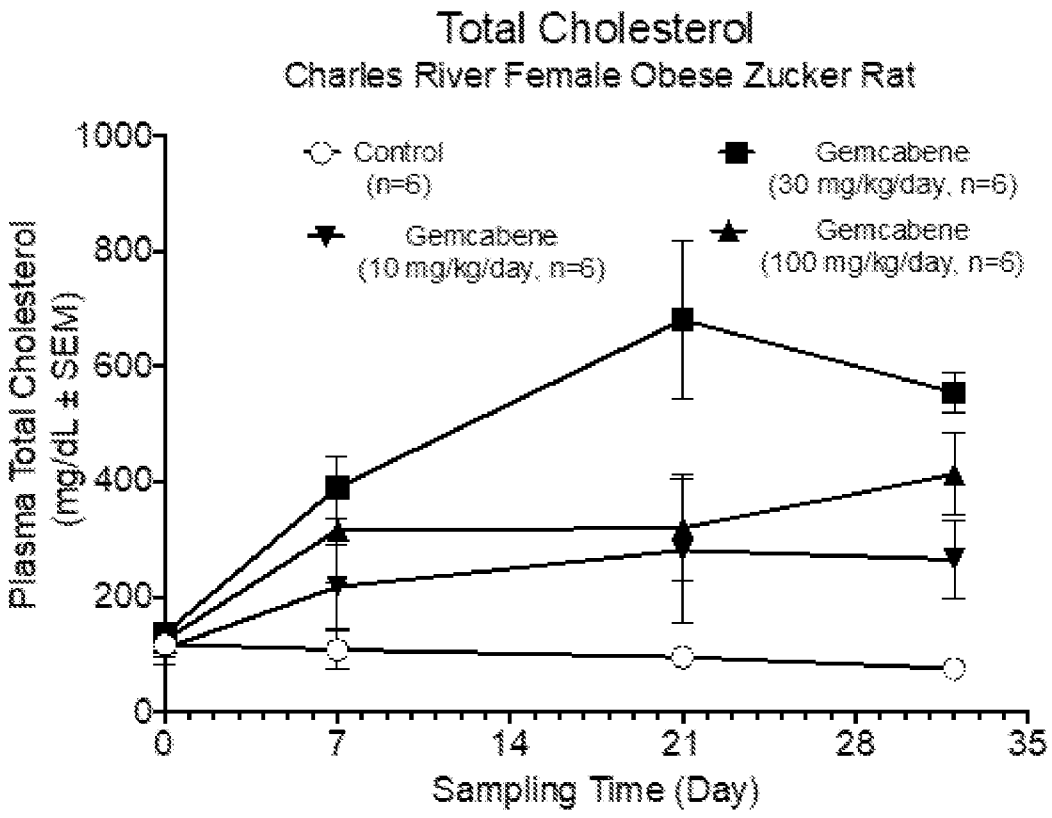

Total Cholesterol
Charles River Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (10 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma Total Cholesterol (mg/dL ± SEM)
1000
800
600
400
200
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 2A

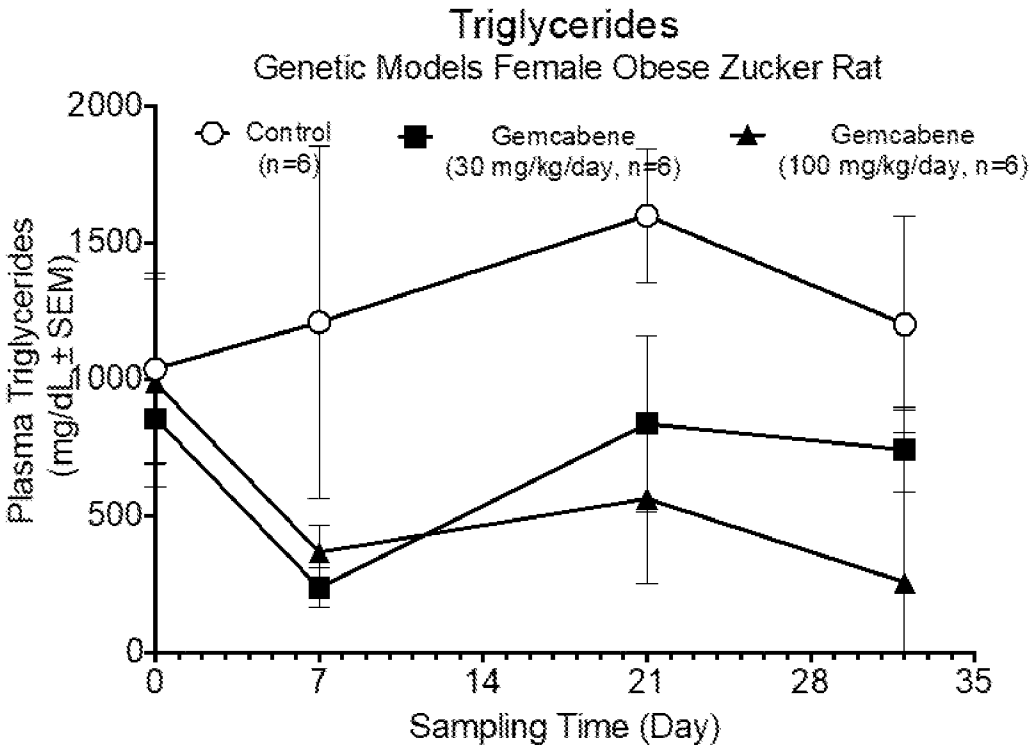

Triglycerides
Genetic Models Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma Triglycerides (mg/dL ± SEM)
2000
1500
1000
500
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 2B

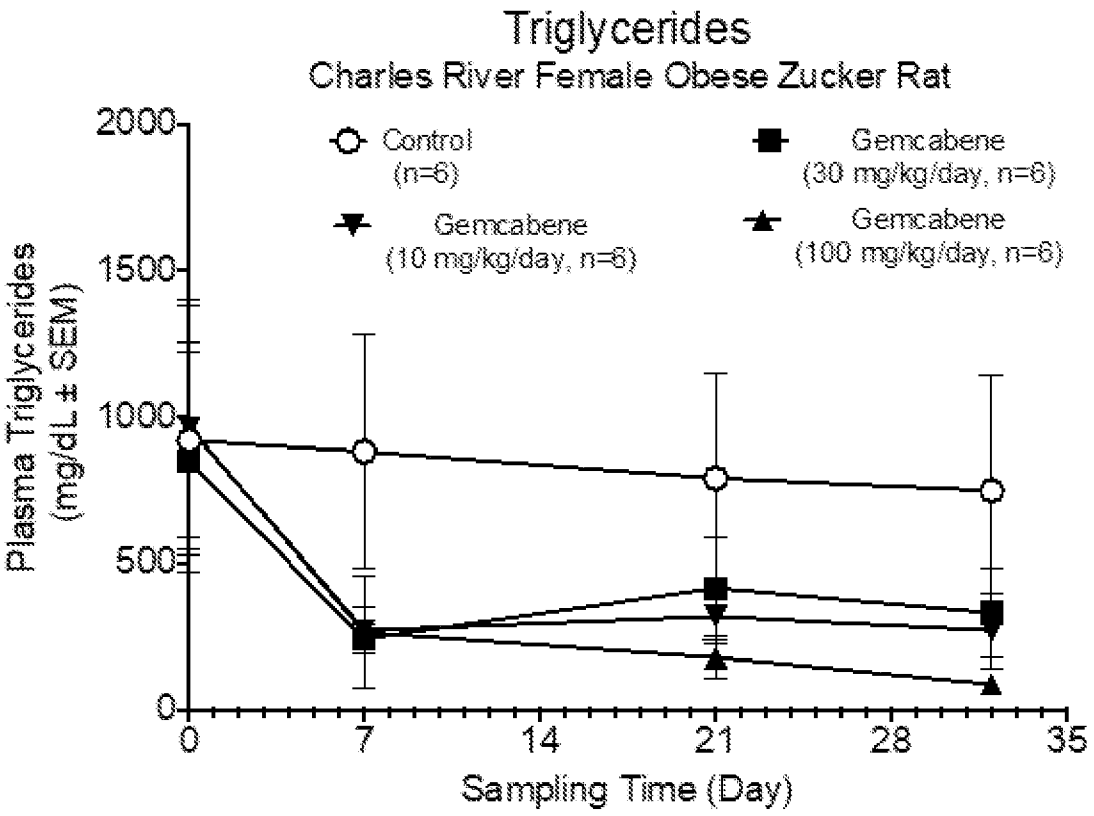

Triglycerides
Charles River Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (10 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma Triglycerides (mg/dL ± SEM)
2000
1500
1000
500
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 3A

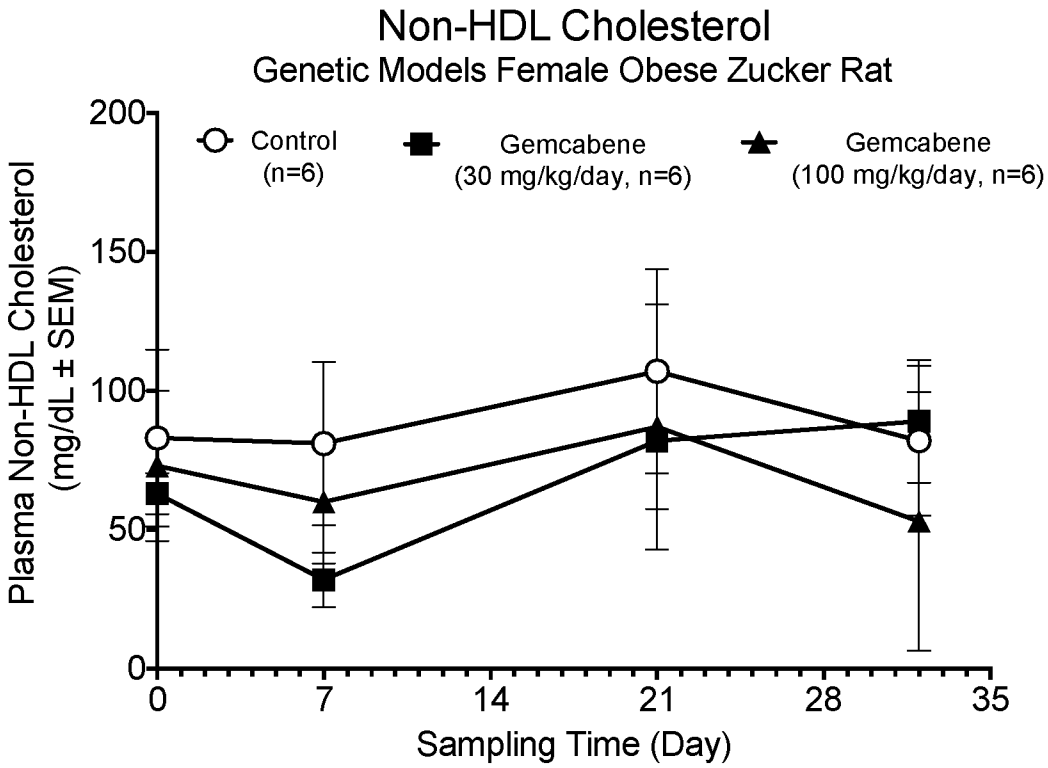

Non-HDL Cholesterol
Genetic Models Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma Non-HDL Cholesterol (mg/dL ± SEM)
200
150
100
50
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 3B

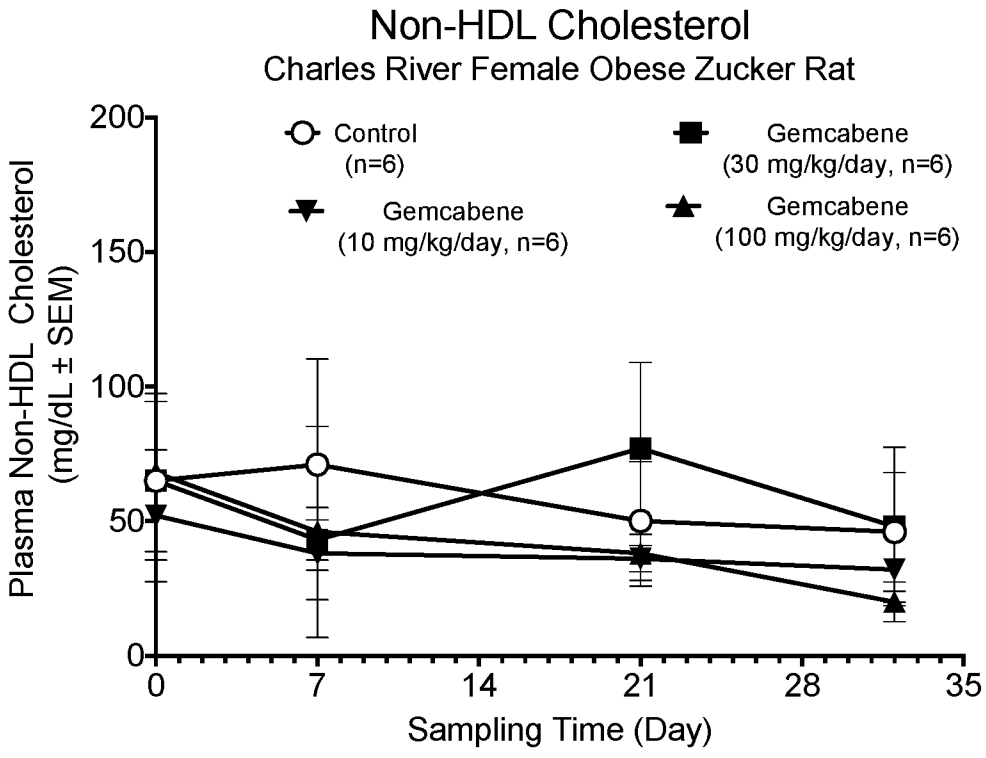

Non-HDL Cholesterol
Charles River Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (10 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma Non-HDL Cholesterol (mg/dL ± SEM)
200
150
100
50
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 4A

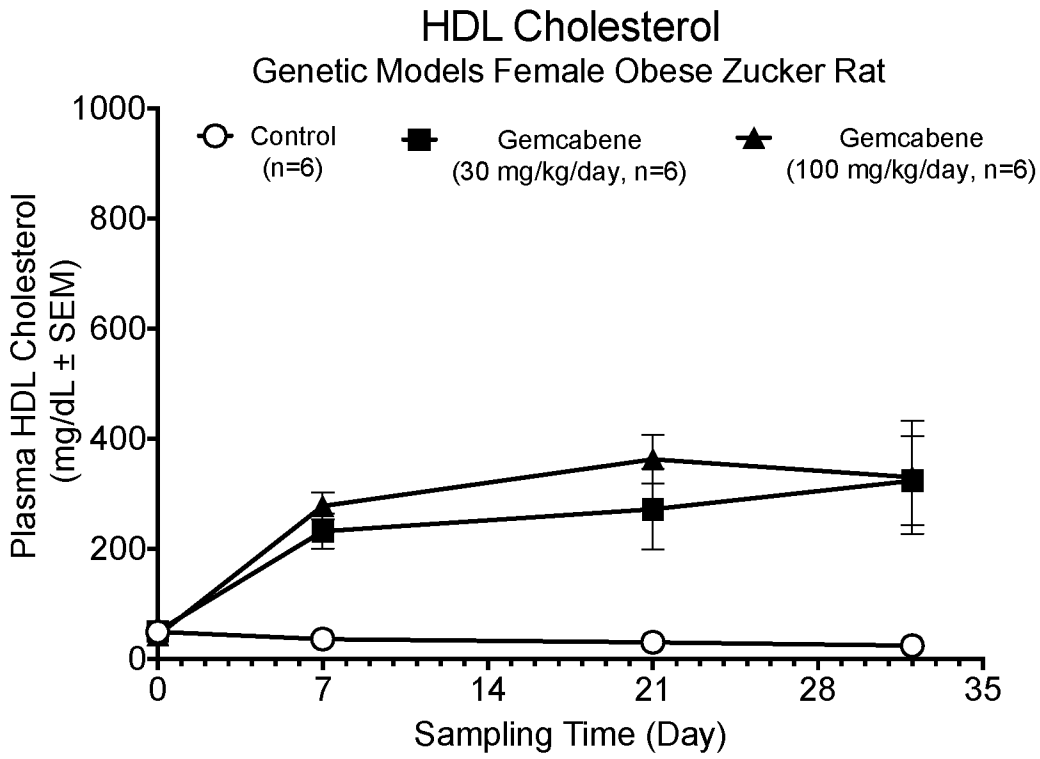

HDL Cholesterol
Genetic Models Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma HDL Cholesterol (mg/dL ± SEM)
1000
800
600
400
200
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 4B

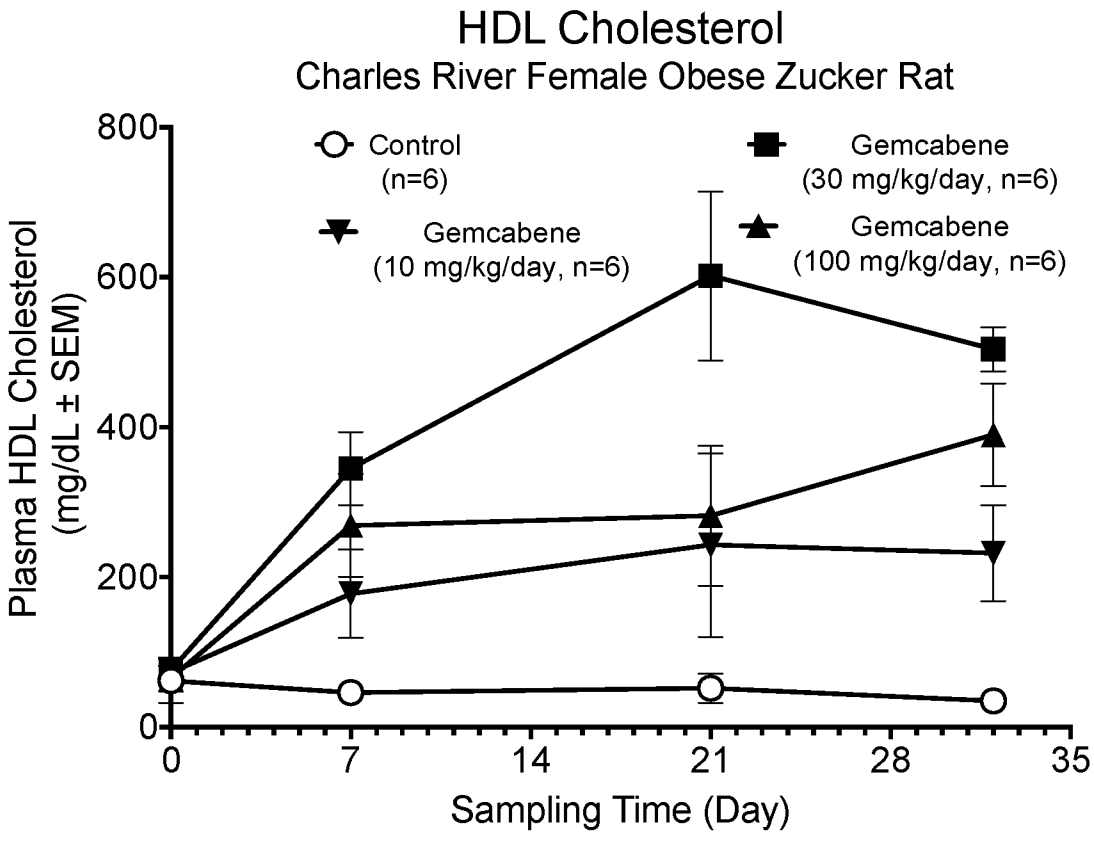

HDL Cholesterol
Charles River Female Obese Zucker Rat
Control (n=6)
Gemcabene (30 mg/kg/day, n=6)
Gemcabene (10 mg/kg/day, n=6)
Gemcabene (100 mg/kg/day, n=6)
Plasma HDL Cholesterol (mg/dL ± SEM)
800
600
400
200
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 5A

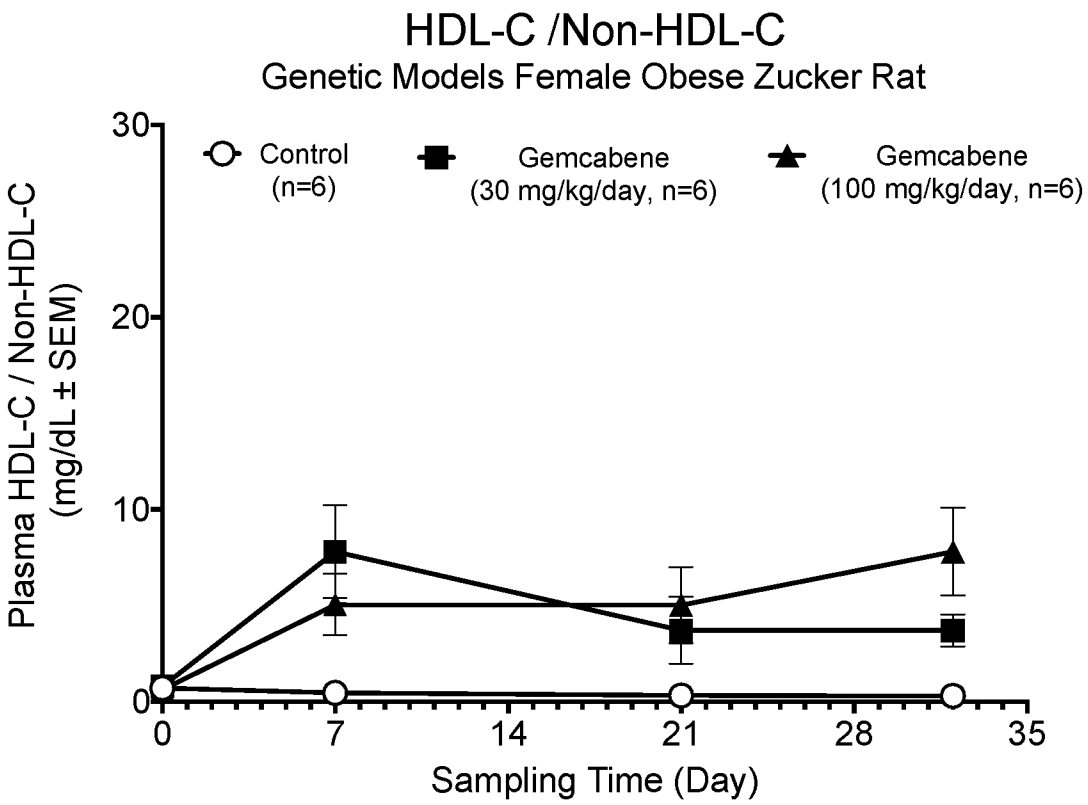

HDL-C /Non-HDL-C
Genetic Models Female Obese Zucker Rat
Control
(n=6)
Gemcabene
(30 mg/kg/day, n=6)
Gemcabene
(100 mg/kg/day, n=6)
Plasma HDL-C / Non-HDL-C
(mg/dL ± SEM)
30
20
10
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 5B

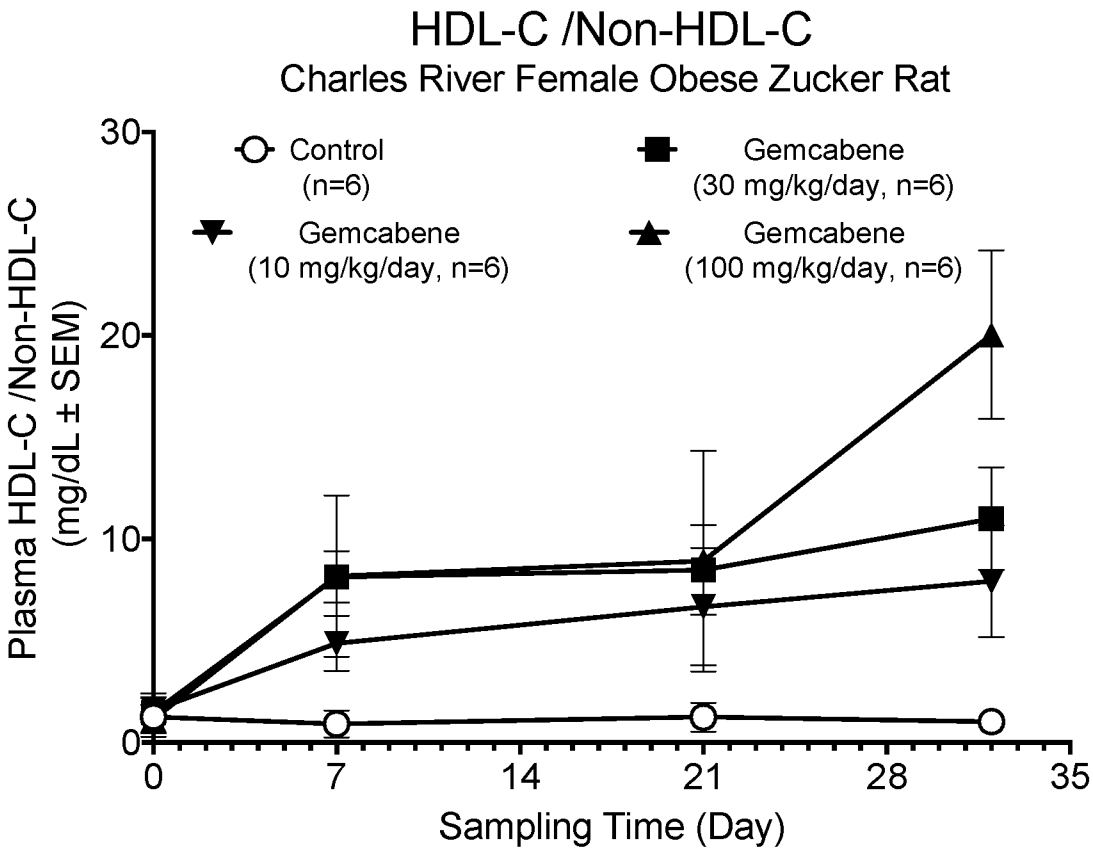

HDL-C /Non-HDL-C
Charles River Female Obese Zucker Rat
Control
(n=6)
Gemcabene
(30 mg/kg/day, n=6)
Gemcabene
(10 mg/kg/day, n=6)
Gemcabene
(100 mg/kg/day, n=6)
Plasma HDL-C /Non-HDL-C
(mg/dL ± SEM)
30
20
10
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 6A

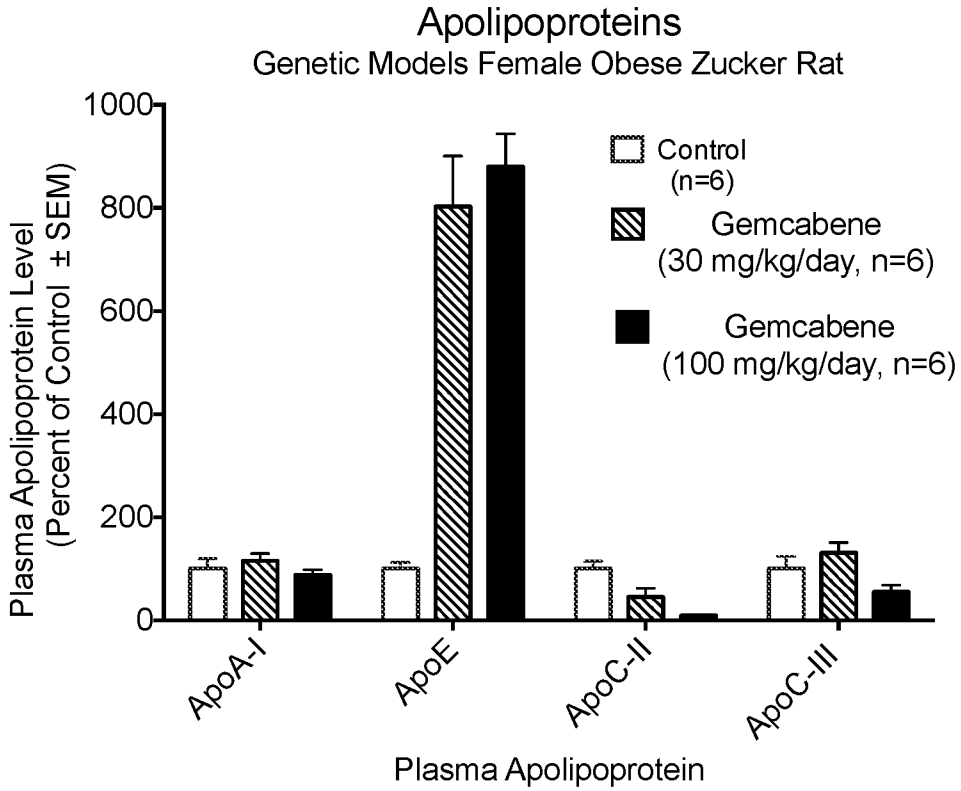

Apolipoproteins
Genetic Models Female Obese Zucker Rat
Plasma Apolipoprotein Level
(Percent of Control ± SEM)
1000
800
600
400
200
0
Control
(n=6)
Gemcabene
(30 mg/kg/day, n=6)
Gemcabene
(100 mg/kg/day, n=6)
ApoA-I
ApoE
ApoC-II
ApoC-III
Plasma Apolipoprotein

FIG. 6B

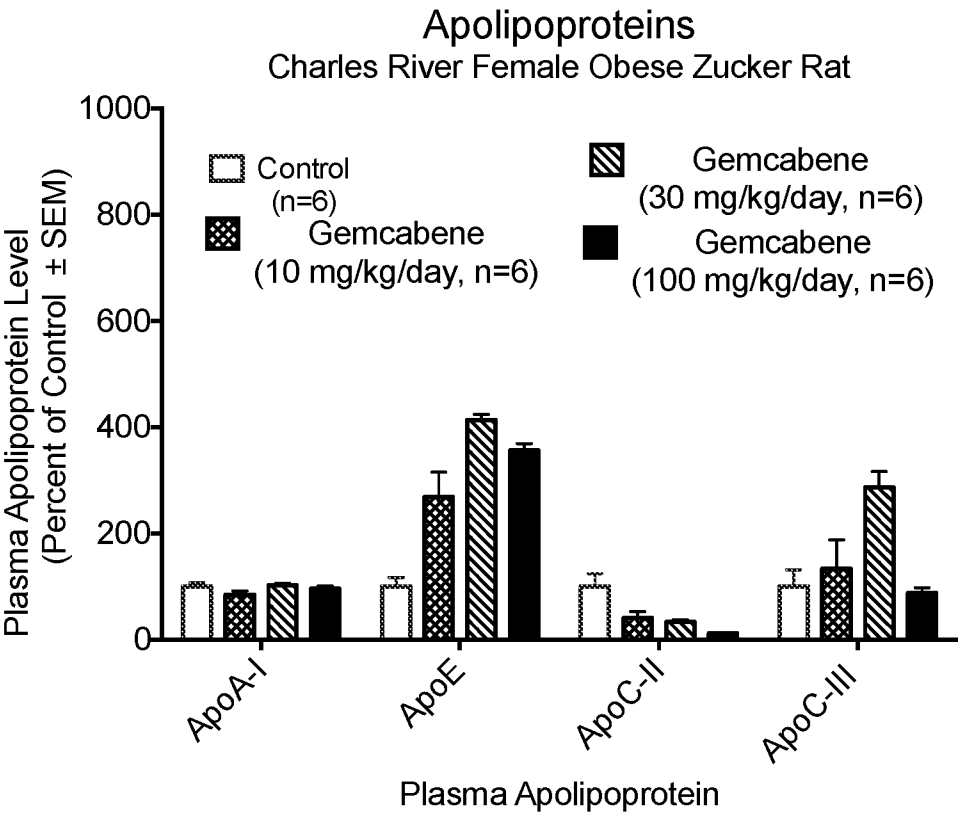

Apolipoproteins
Charles River Female Obese Zucker Rat
Plasma Apolipoprotein Level
(Percent of Control ± SEM)
1000
800
600
400
200
0
Control
(n=6)
Gemcabene
(10 mg/kg/day, n=6)
Gemcabene
(30 mg/kg/day, n=6)
Gemcabene
(100 mg/kg/day, n=6)
ApoA-I
ApoE
ApoC-II
ApoC-III
Plasma Apolipoprotein

FIG. 7A

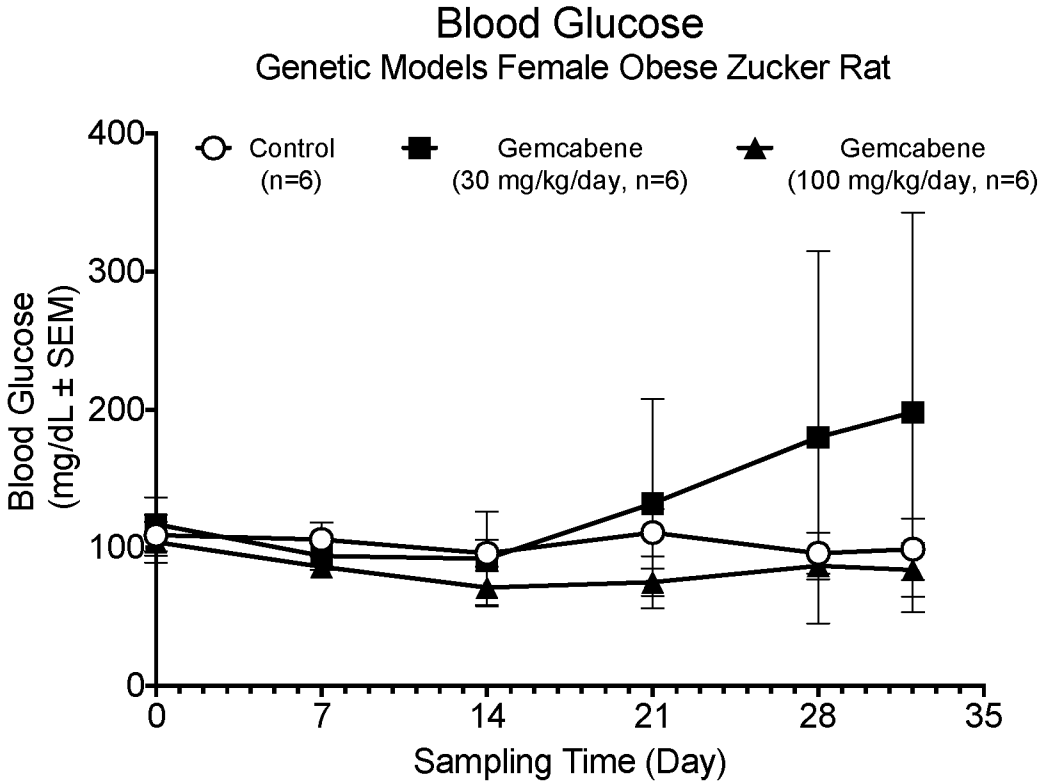

Blood Glucose
Genetic Models Female Obese Zucker Rat
Control
(n=6)
Gemcabene
(30 mg/kg/day, n=6)
Gemcabene
(100 mg/kg/day, n=6)
Blood Glucose
(mg/dL ± SEM)
400
300
200
100
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 7B

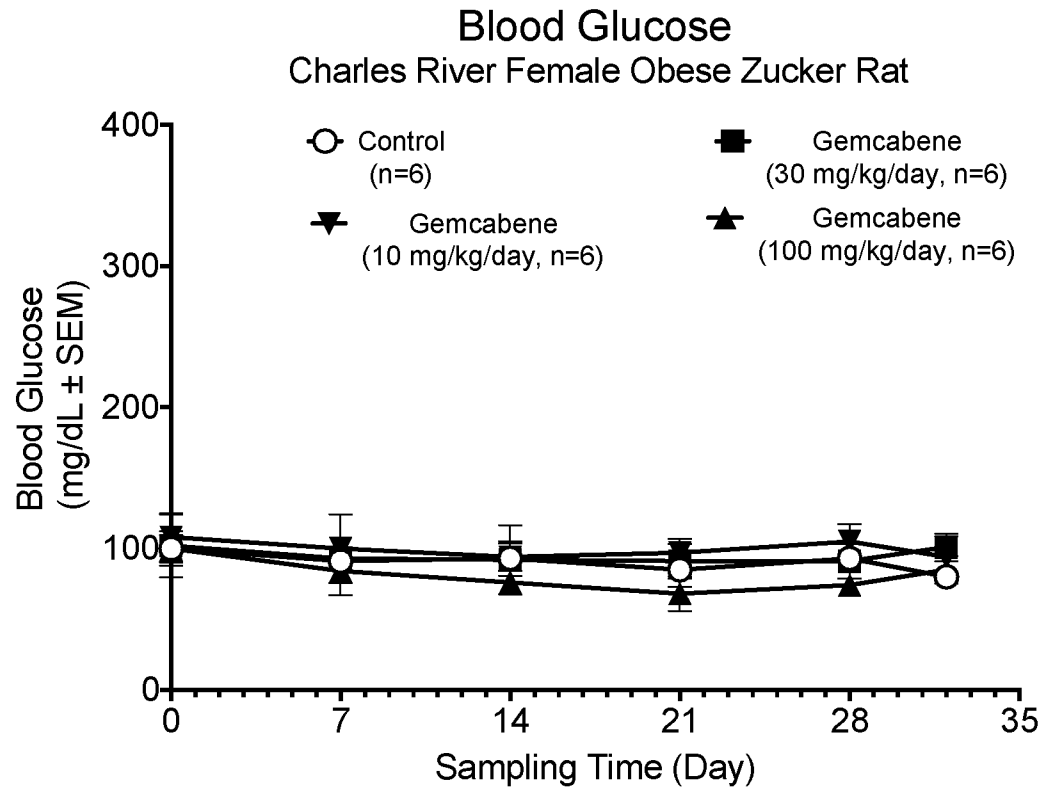

Blood Glucose
Charles River Female Obese Zucker Rat
Control
(n=6)
Gemcabene
(30 mg/kg/day, n=6)
Gemcabene
(10 mg/kg/day, n=6)
Gemcabene
(100 mg/kg/day, n=6)
Blood Glucose
(mg/dL ± SEM)
400
300
200
100
0
0
7
14
21
28
35
Sampling Time (Day)

FIG. 8A

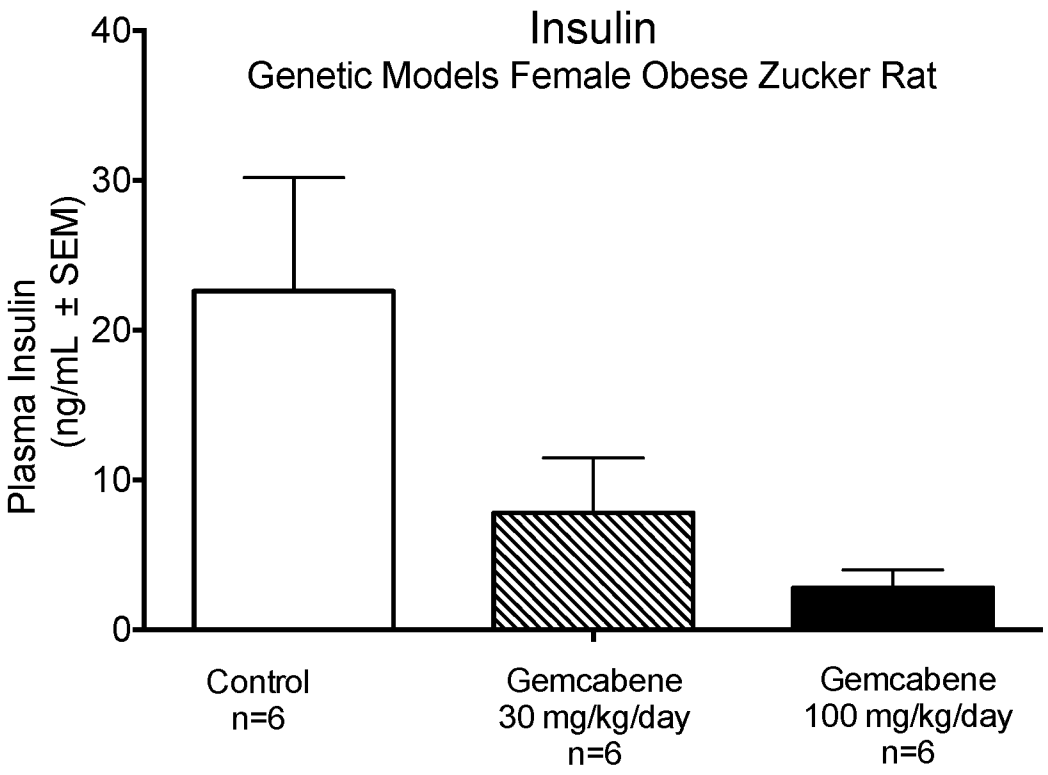

Insulin
Genetic Models Female Obese Zucker Rat
Plasma Insulin (ng/mL ± SEM)
40
30
20
10
0
Control n=6
Gemcabene 30 mg/kg/day n=6
Gemcabene 100 mg/kg/day n=6

FIG. 8B

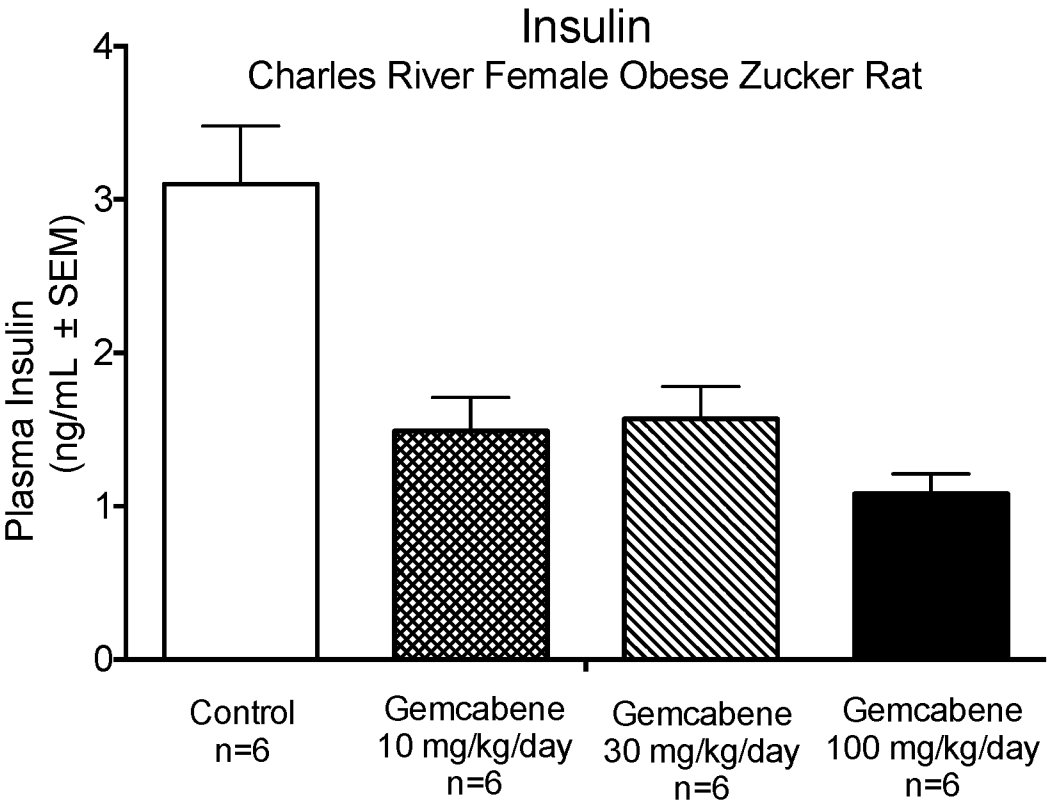

Insulin
Charles River Female Obese Zucker Rat
Plasma Insulin (ng/mL ± SEM)
4
3
2
1
0
Control n=6
Gemcabene 10 mg/kg/day n=6
Gemcabene 30 mg/kg/day n=6
Gemcabene 100 mg/kg/day n=6

FIG. 9A

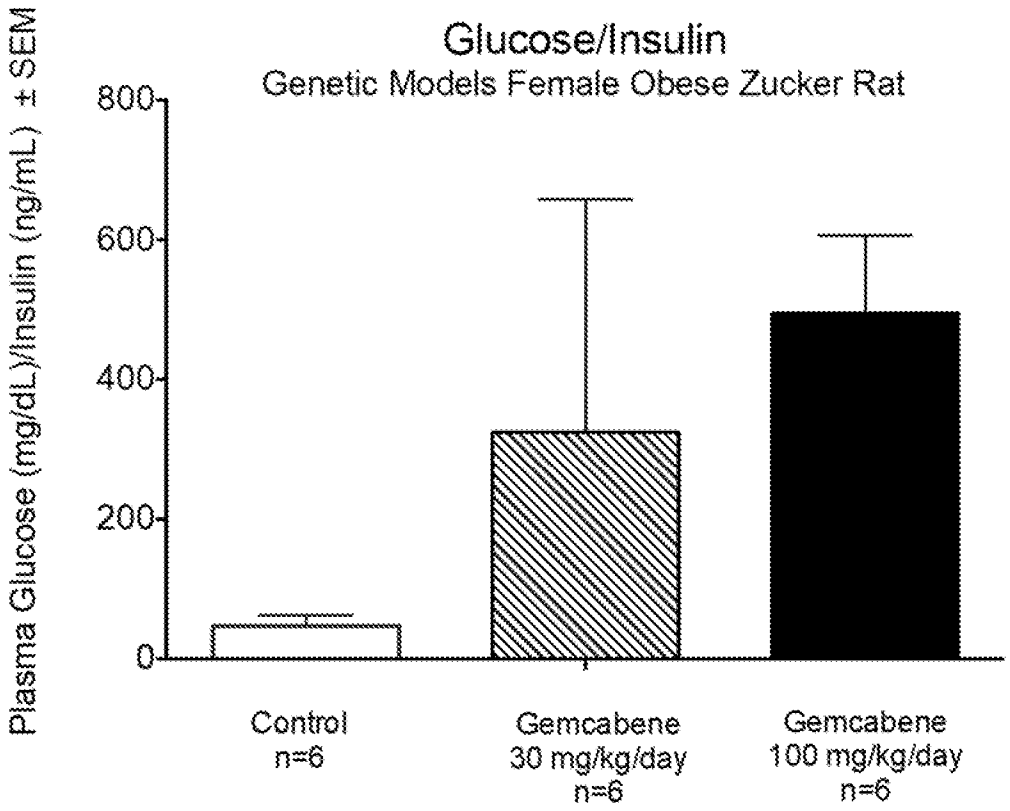

Glucose/Insulin
Genetic Models Female Obese Zucker Rat
Plasma Glucose (mg/dL)/Insulin (ng/mL) ± SEM
800
600
400
200
0
Control
n=6
Gemcabene
30 mg/kg/day
n=6
Gemcabene
100 mg/kg/day
n=6

FIG. 9B

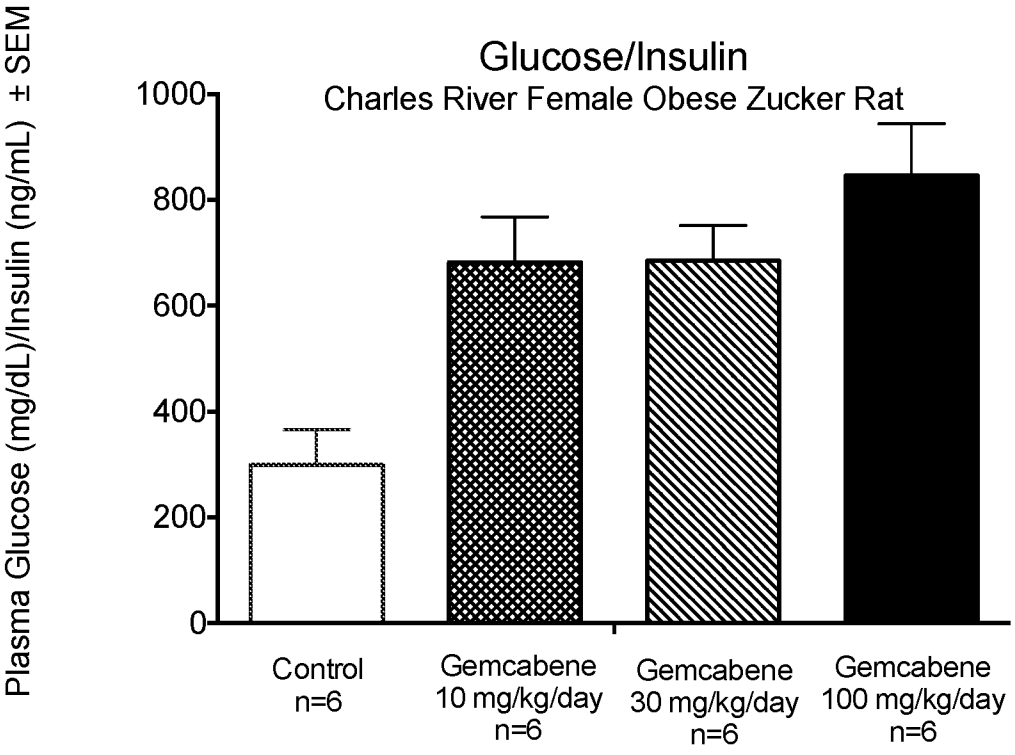

Glucose/Insulin
Charles River Female Obese Zucker Rat
Plasma Glucose (mg/dL)/Insulin (ng/mL) ± SEM
1000
800
600
400
200
0
Control
n=6
Gemcabene
10 mg/kg/day
n=6
Gemcabene
30 mg/kg/day
n=6
Gemcabene
100 mg/kg/day
n=6

FIG. 10A

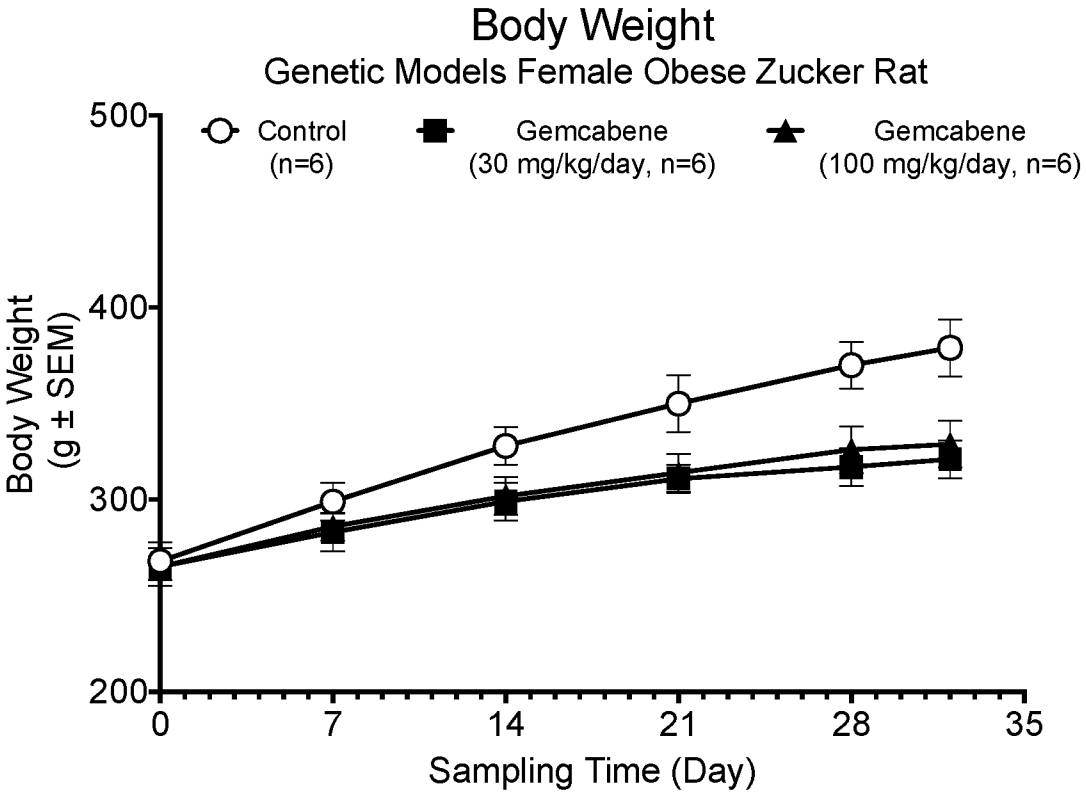


FIG. 10B

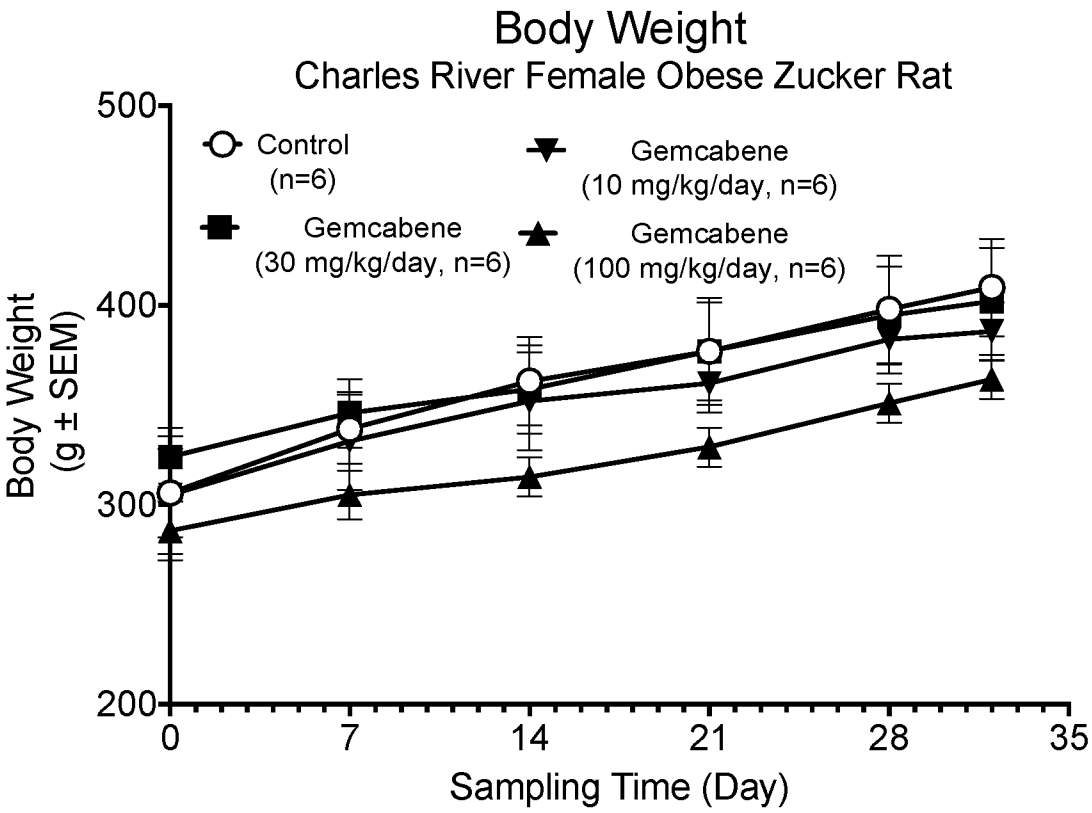


FIG. 11A

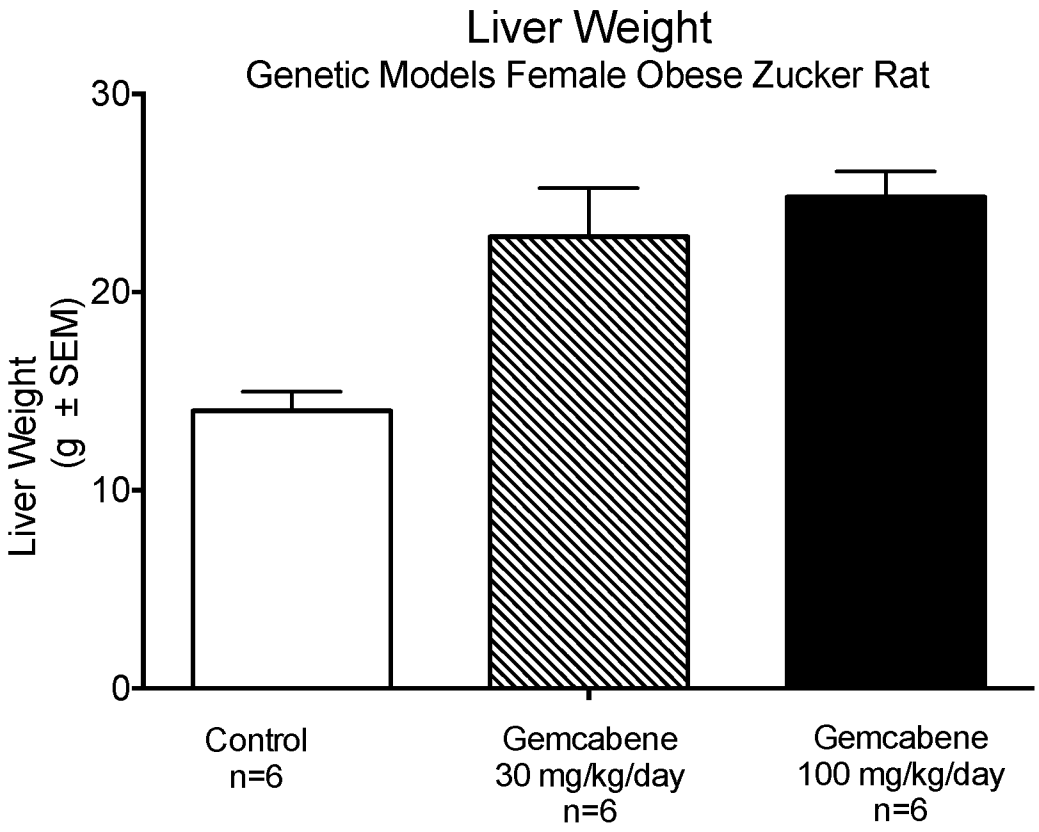


FIG. 11B

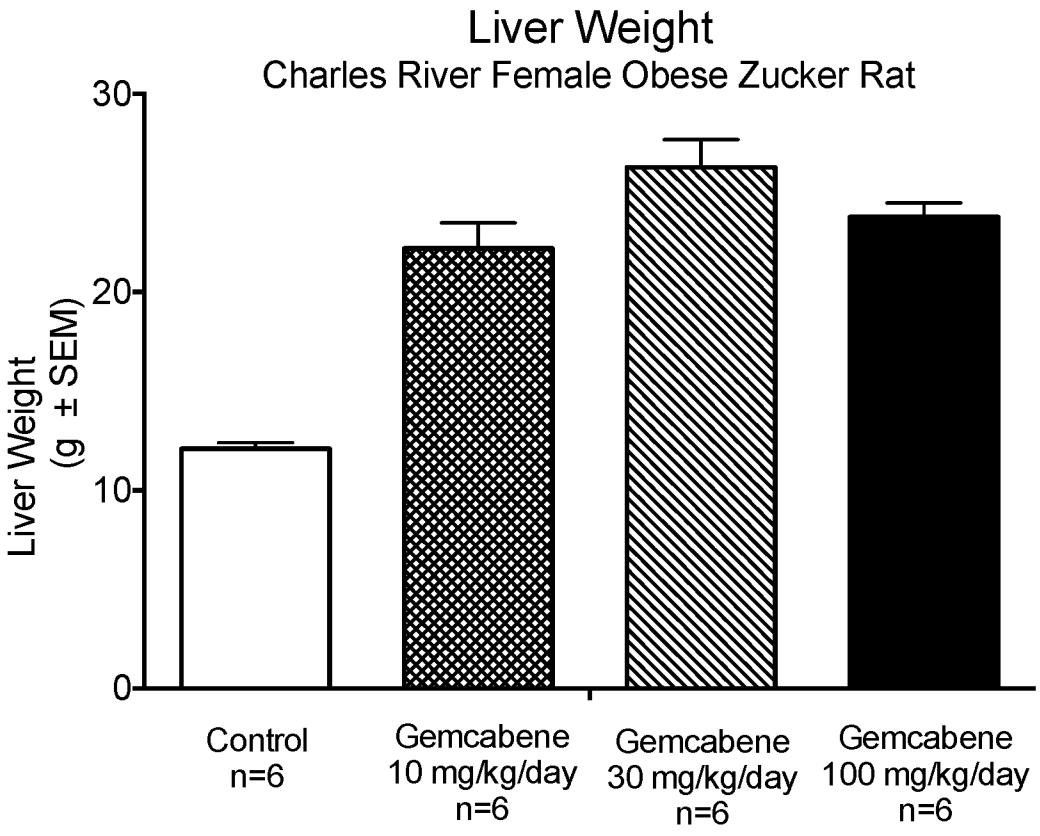


FIG. 12A

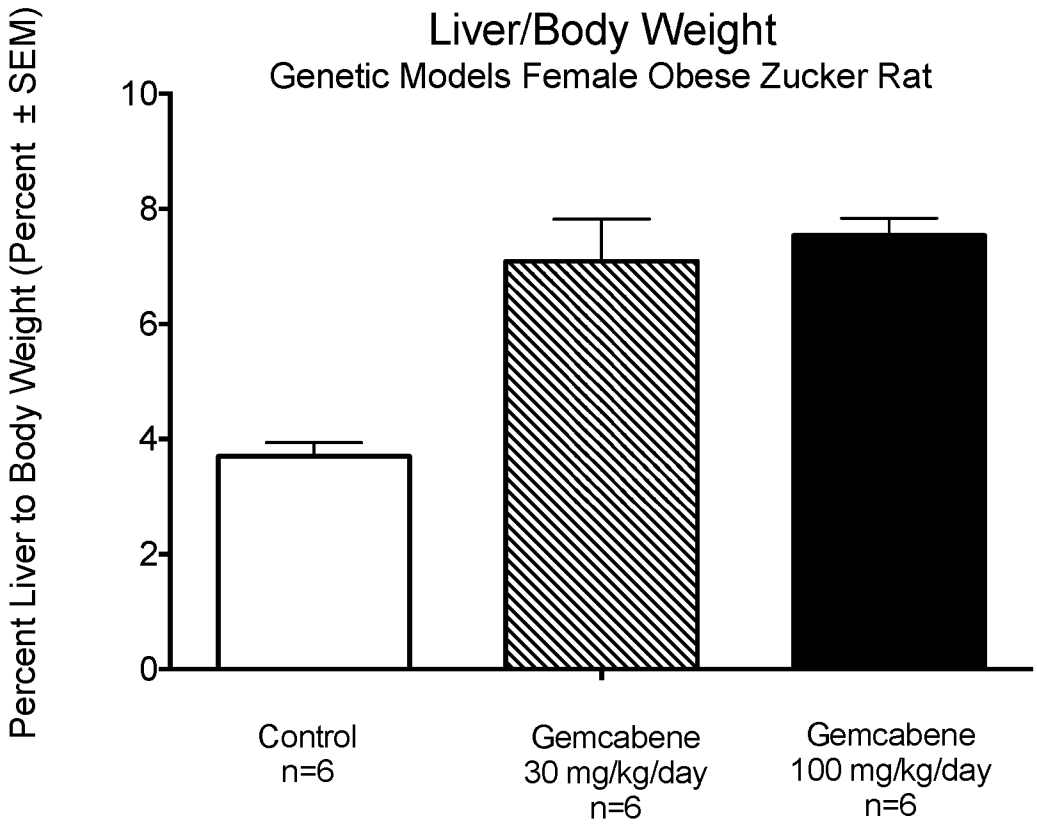


FIG. 12B

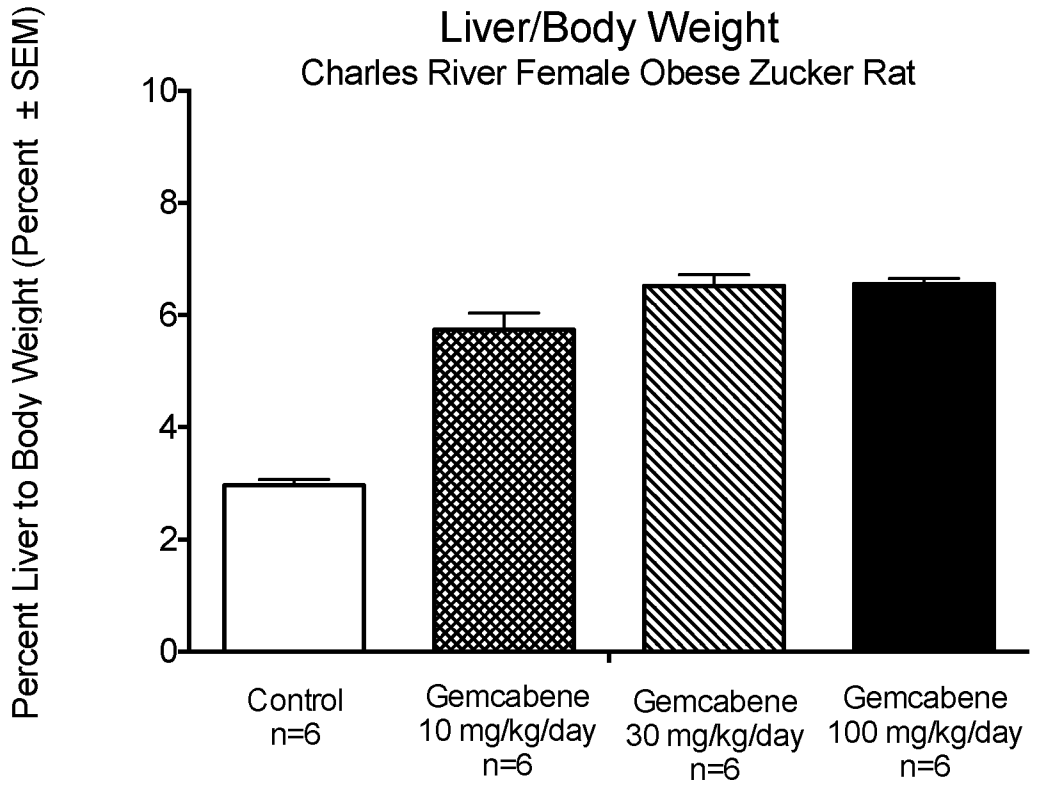


FIG. 13A

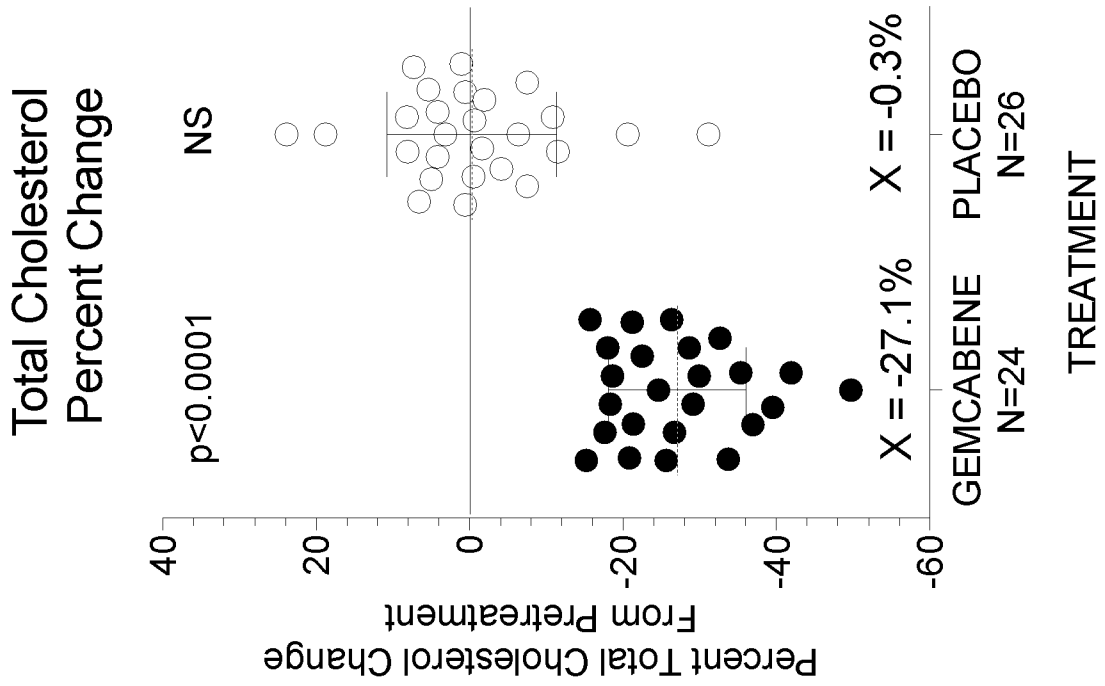


FIG. 13B

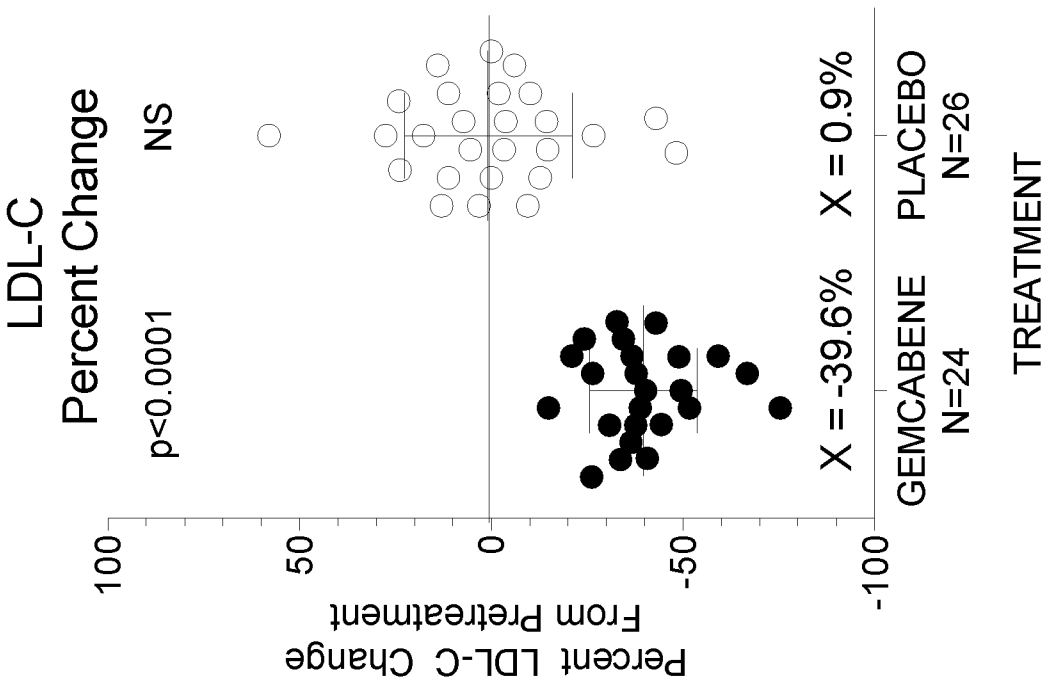


FIG. 13C

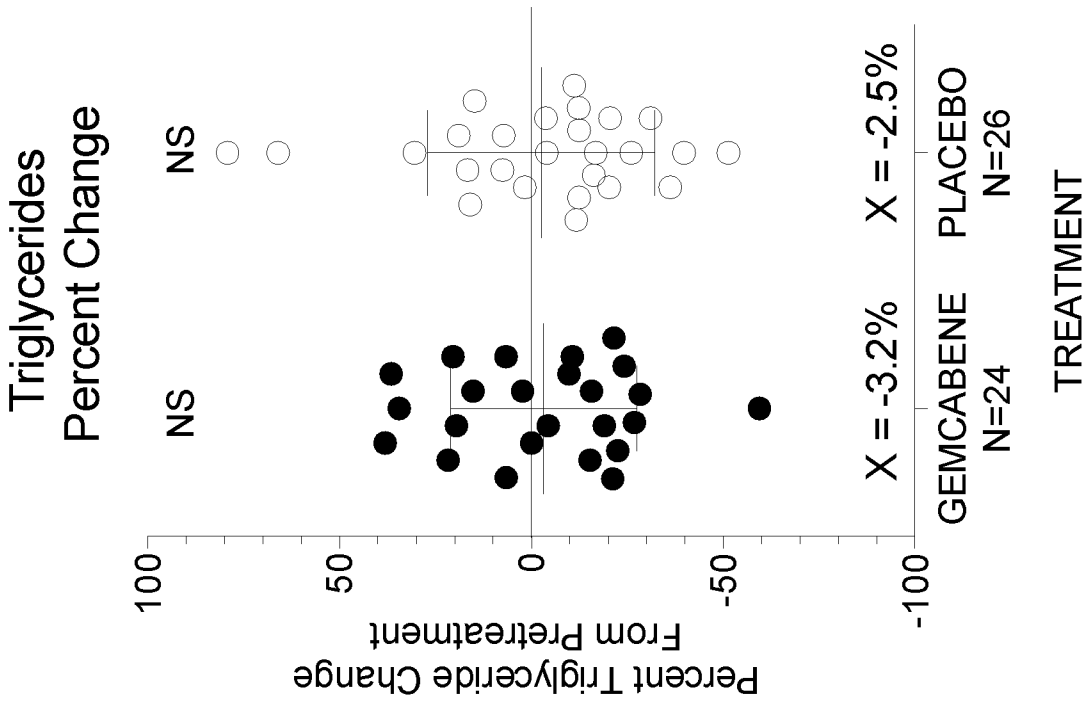
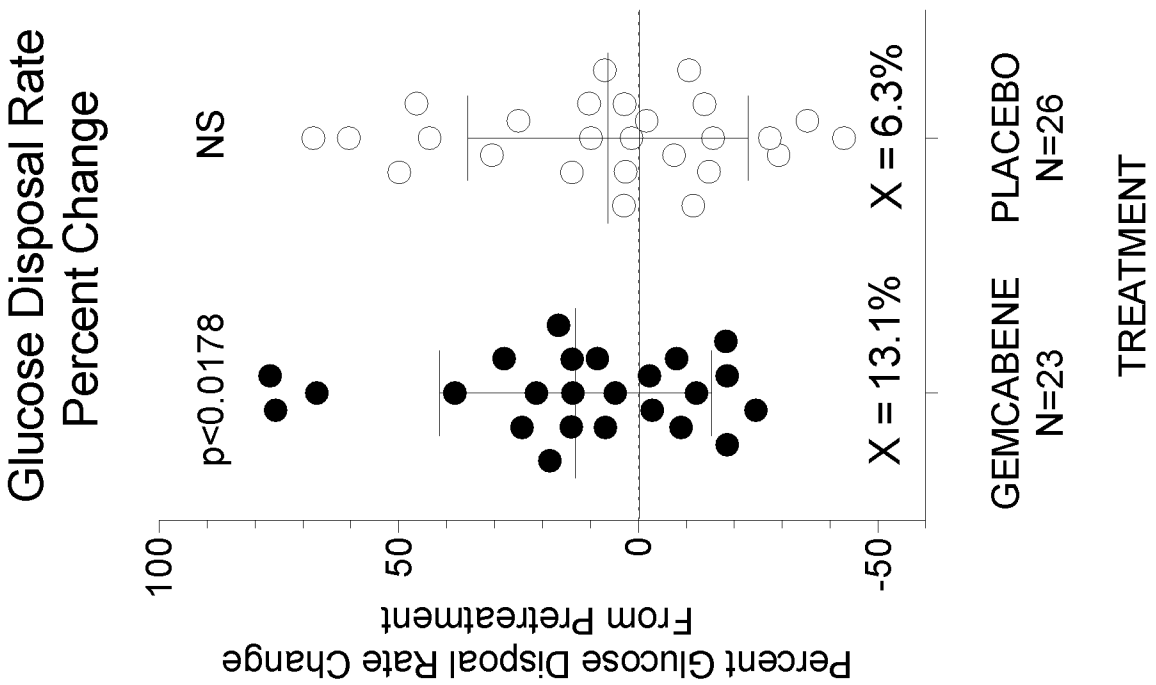


FIG. 13D



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/21093

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 229/08, C07C 229/20, C07C 229/22 (2018.01)
CPC - C07B 2200/07, C07C 229/08, C07C 229/20

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)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/0137584 A1 (Gemphire Therapeutics Inc.,) 19 May 2016 (19.05.2016); Abstract, para[0002], para[0006], para[0112], para[0117], para[0118], para[0120], para[0247]	1-5, 19-21
X	US 5,648,387 A (Bisgaier et al.) 15 July 1997 (15.07.1997); FIG-1, col1, col6, col7, col12, col13	34-43
A	Hakeem et al. 'HIV-associated lipodystrophy - a new metabolic syndrome', The British Journal of Diabetes & Vascular Disease, 01 May 2008 (01.05.2008), Vol.8, pages129-134; p133	1
A	Chait et al. 'Lipodystrophy with Hyperlipidaemia: The Role of Insulin in Very Low Density Lipoprotein Over?]Synthesis', Clinical Endocrinology, February 1979, Vol.10, pages173-178; Summary, p174	19-21
A	Hardy et al. 'What causes the insulin resistance underlying obesity?', Current Opinion in Endocrinology & Diabetes and Obesity, April 2012, Vol.19, pages81-87; p82	34
A	US 2010/0048545 A1 (Jette et al.) 25 February 2010 (25.02.2010); entire document	1-5, 19-21, 34-43
A	US 2013/0116234 A1 (Hoffmann-La Roche Inc.) 09 May 2013 (09.05.2013); entire document	1-5, 19-21, 34-43

☐ Further documents are listed in the continuation of Box C. ☐ 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
26 April 2018	16 MAY 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/21093

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

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

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

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

3. ☒ Claims Nos.: 6-18, 22-33, 44-60
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.