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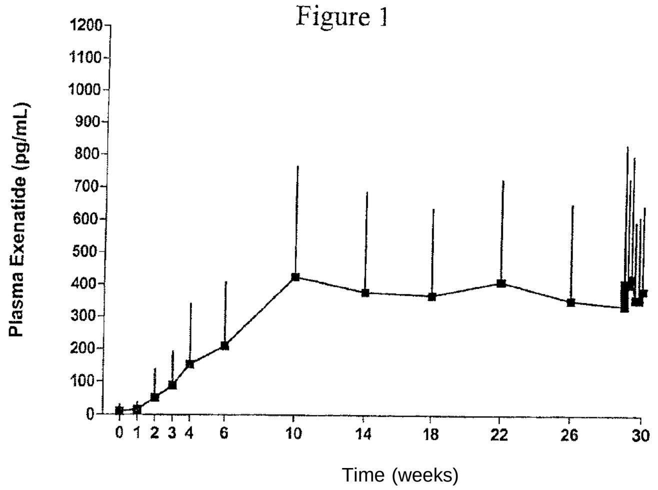
[Continued on next page]

(54) Title: EXENDINS TO LOWER CHOLESTROL AND TRIGLYCERIDES

Figure 1



(57) Abstract: Provided herein are pharmaceutical formulations containing exendins, exendin agonists, or exendin analog agonists that are administered at therapeutic plasma concentration levels over a sustained period of time to lower total cholesterol levels; to lower LDL-cholesterol levels; to lower triglyceride levels; to treat dyslipidemia; to treat and slow the progression of atherosclerosis; and to treat, prevent, and reduce the risk of heart attacks and strokes in patients. In the pharmaceutical formulations and methods of the invention, the exendin may be exendin-4, an exendin-4 agonist, or an exendin-4 analog agonist. The pharmaceutical formulations may be polymer-based pharmaceutical formulations that may be administered once weekly. An exemplary pharmaceutical formulation comprises 5% (w/w) of exenatide, about 2% (w/w) of sucrose, and about 93% (w/w) of a poly(lactide-co- glycolide) polymer, wherein the poly(lactide-co-glycolide) polymer is in the form of niicroshperes encapsulating the exenatide.

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EXENDINS TO LOWER CHOLESTEROL AND TRIGLYCERIDES

FIELD OF THE INVENTION

[001] This application claims priority to US Application No. 61/054,883 filed May 21, 2008, the disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

[002] The invention relates to the field of medicine, such as the use of exendins, exendin agonists, and exendin analog agonists to lower plasma lipid levels and improve cardiovascular health in patients.

BACKGROUND OF THE INVENTION

[003] Research from experimental animals, laboratory investigations, epidemiology and genetic forms of hypercholesterolemia indicate that elevated cholesterol is a major cause of coronary heart disease. The Framingham Heart Study also established that high blood cholesterol is a risk factor for coronary heart disease. Results of the Framingham study showed that the higher the cholesterol level, the greater the risk of suffering from coronary heart disease. On the other end of the spectrum, coronary heart disease is generally uncommon at total cholesterol levels below 150 milligrams per deciliter (mg/dL). A series of more recent trials of cholesterol lowering using statin drugs has demonstrated that lowering total cholesterol and low density lipoprotein (LDL) cholesterol reduces the chances of suffering a major coronary event, such as myocardial infarction, angina, or coronary artery procedures (e.g., angioplasty, bypass surgery). Grundy et al, *Circulation*, 110:227-239 (2004).

[004] Total serum cholesterol contains three major classes of lipoproteins: about 60-70% LDL-cholesterol; about 20-30% high density lipoprotein (HDL) cholesterol; and about 10-15% very low density lipoprotein (VLDL) cholesterol. While LDL is the primary target for cholesterol lowering therapy, HDL and VLDL play a role in atherosclerosis.

[005] The American Heart Association endorses the National Cholesterol Education Program (NCEP) guidelines for the detection of high cholesterol and the guidelines for healthy fasting lipoproteins. Total cholesterol levels of less than 200 mg/dL are desirable, while 240 mg/dL and above are high. HDL cholesterol levels of 60 mg/dL and above are considered protective against heart disease, while levels less than 40 mg/dL are a major risk factor for heart disease. LDL cholesterol levels of 129 mg/dL or less are near or at optimal, while 160 mg/dL or more are high. Triglyceride levels of less than 150 mg/dL are normal,

while 200 mg/dL and above are high. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report, National Institutes of Health, NIH Publication No. 02-5215 (2002).

[006] Current treatments to reduce elevated triglycerides, total cholesterol, and LDL-cholesterol in patients include small molecule oral monotherapy and combination therapy. The first drug of choice is generally an HMG CoA reductase inhibitor, i.e., statin. Exemplary statins include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Another class of drugs is the bile ace sequestrants, such as colesevelam, cholestyramine, and colestipol. Yet another class of drugs is the fibrates, such as fenofibrate, clofibrate, and gemfibrozil. Other drugs used to treat high cholesterol include ezetimibe, nicotinic acid, and probucol. Several of these drugs are used in combination therapy, such as ADVICOR® (lovastatin and niacin by Abbott Laboratories); CADUET® (atorvastatin and amlodipine by Pfizer, Inc.); and VYTORIN™ (simvastatin and ezetimibe by Merck and Schering Plough).

[007] Exendins are peptides that are found in the saliva of the GiIa monster, a lizard endogenous to Arizona, and the Mexican Beaded Lizard. Exendin-3 is present in the saliva of *Heloderma horridum,* and exendin-4 is present in the saliva of *Heloderma suspectum.* Eng et al, *J. Biol. Chem.,* 265:20259-62 (1990); Eng et al, *J. Biol. Chem.,* 267:7402-05 (1992). Exendins have some amino acid sequence similarity to several members of the glucagon-like peptide (GLP) family. For example, exendin-4 as 53% sequence identity with glucagon-like peptide 1 (GLP-I). Gδke et al, *J. Biol Chem.,* 268:19650-55 (1993). However, exendin-4 is transcribed from a distinct gene, not the GiIa monster homolog of the mammalian proglucagon gene from which GLP-I is expressed. Additionally, exendin-4 is not an analog of GLP-I. The structure of the synthetic exendin-4 peptide was not created by sequential modification of the structure of GLP-I. Nielsen et al, *Current Opinion in Investigational Drugs,* 4(4):401-405 (2003); Nielsen et al, *Regulatory Peptides,* 117:77-88 (2004).

[008] Exendin-4 is a potent GLP-I receptor agonist in vitro. The peptide also stimulates somatostatin release and inhibits gastrin release in isolated stomachs. Gδke et al, *J. Biol Chem.,* 268:19650-55 (1993); Schepp et al, *Eur. J. Pharmacol,* 69:183-91 (1994); Eissele et al, *Life ScL,* 55:629-34 (1994). Exendin-3 and exendin-4 were found to be GLP-I receptor agonists in stimulating cAMP production in, and amylase release from, pancreatic acinar cells. Malhotra et al, *Regulatory Peptides,* 41:149-56 (1992); Raufman et al, *J. Biol. Chem.,* 267:21432-37 (1992); Singh et al, *Regulatory Peptides,* 53:47-59 (1994). The use of

the insulinotropic activities of exendin-3 and exendin-4 for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed. US Patent No. 5,424,286. Synthetic exendin-4, generically known as exenatide, is commercially available as BYETTA® (Amylin Pharmaceuticals, Inc. and Eli Lilly & Company). Sustained administration of exendins has been proposed. US Publication No. 2004/0053819.

[009] The need exists for new and improved pharmaceutical compositions and formulations to reduce total cholesterol levels, LDL cholesterol levels, and triglyceride levels in patients in need thereof, to treat dyslipidemia, and atherosclerosis in patients in need thereof, and to reduce the risk of atherosclerosis, heart attacks and strokes in patients in need thereof. Pharmaceutical compositions and formulations that meet the needs of these patients are described herein.

SUMMARY OF THE INVENTION

[010] Provided herein are methods for lowering total cholesterol levels, LDL-cholesterol levels, and triglyceride levels (e.g., fasting triglyceride levels) in patients in need thereof by administering to the patients formulations comprising sufficient amounts of at least one exendin, exendin agonist, or exendin analog agonist to maintain steady state average, geometric mean, or minimum plasma concentrations of the exendins, exendin agonists, or exendin analog agonists effective to reduce the total cholesterol levels, LDL-cholesterols levels, or triglyceride levels (e.g., fasting triglyceride levels) in the patients.

[011] Provided herein are methods for treating dyslipidemia and atherosclerosis in patients in need thereof by administering to the patients formulations comprising sufficient amounts of at least one exendin, exendin agonist or exendin analog agonist to maintain steady state average, geometric mean, or minimum plasma concentrations of the exendins, exendin agonists, or exendin analog agonists effective to treat dyslipidemia or atherosclerosis in the patients.

[012] Provided herein are methods for preventing, treating, and reducing the risk of heart attacks and strokes in patients in need thereof by administering to the patients formulations comprising sufficient amounts of at least one exendin, exendin agonist, or exendin analog agonist to maintain steady state average, geometric mean, or minimum plasma concentrations of the exendins, exendin agonists, or exendin analog agonists effective to treat prevent, treat, or reduce the risk of heart attacks and strokes in the patients.

[013] Provided herein are the use of exendins, exendin agonists, and exendin analog agonists in the manufacture of medicaments for use in lowering total cholesterol levels, LDL-cholesterol levels, and triglyceride levels (e.g., fasting triglyceride levels). Also provided

herein are the uses of exendins, exendin agonists, and exendin analog agonists in the manufacture of medicaments in treating dyslipidemia and atherosclerosis, and in reducing the risk of heart attacks and strokes.

[014] Provided herein are methods of treating diabetes; methods of treating obesity; methods of reducing hemoglobin A_{1C}; and methods of reducing postprandial blood glucose in patients in need thereof by administering to the patients a pharmaceutical formulation comprising at least one exendin, exendin agonist or exendin analog agonist in an amount sufficient to maintain a steady state geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist at a level of about 145 pg/mL to about 700 pg/mL. In other embodiments, the steady state geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist is about 175 pg/mL to about 650 pg/mL; about 200 pg/mL to about 600 pg/mL; about 200 pg/mL to about 400 pg/mL; or about 300 pg/mL. In other embodiments, the formulation contains the exendin, exendin agonist or exendin analog agonist in an amount of about 0.01 mg to about 1 mg; or about 0.1 mg.

[015] In one embodiment of the pharmaceutical formulations and methods described herein, the exendin, exendin agonist or exendin analog agonist is exendin-4, an exendin-4 agonist or an exendin-4 analog agonist.

[016] In one embodiment, the pharmaceutical formulations comprise poly(lactide-co-glycolide) polymeric microspheres encapsulating exenatide, where such pharmaceutical formulations comprise about 5% (w/w) exenatide, about 2% (w/w) sucrose, and about 93% (w/w) of the poly(lactide-co-glycolide) polymer.

BRIEF DESCRIPTION OF THE DRAWINGS

[017] **Figure 1.** Plasma exenatide concentrations (mean+SD) over a period of 30 weeks in 128 patients receiving exenatide once weekly. At week 30, the average plasma concentration was 388 pg/mL, and the geometric mean plasma concentration was 300.2 pg/mL.

[018] **Figure 2.** Fasting Triglycerides. **(2A)** Fasting triglycerides (mg/dL) decreased by an average of 42 mg/dL from baseline to week 30 in patients receiving exenatide once weekly. (2B) Fasting triglycerides (mg/dL) decreased by an average of 22 mg/dL from baseline to week 30 in patients receiving exenatide twice daily.

[019] **Figure 3.** Cholesterol. (3A) Total cholesterol decreased by an average of 11.9 mg/dL from baseline to week 30 in patients receiving exenatide once weekly. (3B) Total cholesterol decreased by an average of 3.8 mg/dL from baseline to week 30 in patients receiving exenatide twice daily. (3C) LDL-cholesterol decreased by an average of 4.9 mg/dL

from baseline to week 30 in patients receiving exenatide once weekly. (3D) LDL-cholesterol increased by an average of 1.2 mg/dL from baseline to week 30 in patients receiving exenatide twice daily. (3E) HDL-cholesterol decreased by an average of 0.9 mg/dL from baseline to week 30 in patients receiving exenatide once weekly. (3F) HDL-cholesterol decreased by an average of 1.3 mg/dL from baseline to week 30 in patients receiving exenatide twice daily.

[020] **Figure 4.** Weight loss. (4A) After 30 weeks, the body weight for patients receiving exenatide once weekly decreased by an average of 3.7 kg. (4B) After 30 weeks, the body weight for patients receiving exenatide twice daily decreased by an average of 3.6 kg.

[021] **Figure 5.** Hemoglobin A_1C(HbA_1C). **(A)** HbAic decreased by an average of 1.9% from baseline to week 30 in patients receiving exenatide once weekly. (B) HbAic decreased by an average of 1.5% from baseline to week 30 in patients receiving exenatide BID.

[022] **Figure 6.** Fasting Postprandial Glucose. (A) Fasting postprandial blood glucose decreased by an average of 42 mg/dL from baseline to week 30 in patient receiving exenatide once weekly. (B) Fasting postprandial blood glucose decreased by an average of 25 mg/dL from baseline to week 30 in patient receiving exenatide BID.

DETAILED DESCRIPTION OF THE INVENTION

[023] Provided herein are compositions, medicaments for manufacture, and methods for reducing total cholesterol levels, reducing LDL-cholesterol levels, reducing triglyceride levels, treating dyslipidemia, treating atherosclerosis, and reducing the risk of heart attacks and strokes in patients in need or desirous thereof by administering at least one exendin, exendin agonist, or exendin analog agonist. The methods include the chronic (i.e., sustained) administration of an effective amount of at least one exendin, exendin agonist, or exendin analog agonist to a patient to achieve the desired results as described herein.

[024] Provided herein are methods for lowering total cholesterol levels in patients in need thereof by identifying patients in need of a reduction in total cholesterol levels and administering to the patients a pharmaceutical formulation comprising a sufficient amount of at least one exendin, exendin agonist or exendin analog agonist to maintain a steady state average, geometric mean, or minimum plasma concentration level of the exendin, exendin agonist, or exendin analog agonist effective to reduce the total cholesterol levels in the patient. The total cholesterol levels may be reduced by at least 1 mg/dL; at least 2 mg/dL; at least 3 mg/dL; at least 4 mg/dL; at least 5 mg/dL; at least 6 mg/dL; at least 7 mg/dL; at least 8

mg/dL; or at least 9 mg/dL. In other embodiments, the total cholesterol levels may be reduced by at least 10 mg/dL. In still other embodiments, total cholesterol levels may be reduced by 1 mg/dL to 25 mg/dL; from 5 mg/dL to 25 mg/dL; or from 10 mg/dL to 25 mg/dL. In one embodiment, the patient has a total blood cholesterol level of 200 mg/dL or more. In another embodiment, the patient has a total blood cholesterol level of 240 mg/dL or more. In one embodiment, total blood cholesterol levels are fasting total blood cholesterol levels that are measured after an 8-12 hour fast without oral intake of food or liquids.

[025] Provided herein are methods for lowering LDL-cholesterol levels in a patients in need thereof by identifying patients in need of a reduction in LDL-cholesterol levels and administering to the patients a pharmaceutical formulation comprising a sufficient amount of at least one exendin, exendin agonist or exendin analog agonist to maintain a steady state average, geometric mean, or minimum plasma concentration level of the exendin, exendin agonist, or exendin analog agonist effective to reduce the LDL-cholesterol levels in the patient. The LDL-cholesterol levels may be reduced by at least 1 mg/dL; at least 2 mg/dL; at least 3 mg/dL; at least 4 mg/dL; at least 5 mg/dL; at least 6 mg/dL; at least 7 mg/dL; at least 8 mg/dL; at least 9 mg/dL; or at least 10 mg/dL. In other embodiments, LDL-cholesterol levels may be reduced by 1 mg/dL to 20 mg/dL; from 1 mg/dL to 15 mg/dL; or from 1 mg/dL to 10 mg/dL. In one embodiment, the patient has LDL cholesterol levels of 130 mg/dL or more. In another embodiment, the patient has LDL cholesterol levels of 160 mg/dL or more. In yet another embodiment, the patient has LDL cholesterol levels of 190 mg/dL or more. In one embodiment, LDL cholesterol levels are fasting LDL cholesterol levels that are measured after an 8-12 hour fast without oral intake of food or liquids.

[026] Provided herein are methods for reducing triglyceride levels in patients in need thereof by identifying patients in need of a reduction in triglyceride levels and administering to the patients a pharmaceutical formulation comprising a sufficient amount of at least one exendin, exendin agonist or exendin analog agonist to maintain a steady state average, geometric mean, or minimum plasma concentration level of the exendin, exendin agonist, or exendin analog agonist effective to reduce the triglyceride levels in the patient. In one embodiment, the triglyceride levels are fasting triglyceride levels. Fasting triglyceride levels may be measured after an 8-12 hour fast without oral intake of food or liquids. In one embodiment, the triglyceride levels are reduced by at least 5 mg/dL; at least 10 mg/dL; at least 15 mg/dL; at least 20 mg/dL; at least 25 mg/dL; at least 30 mg/dL; at least 35 mg/dL; at least 40 mg/dL; at least 45 mg/dL; or at least 50 mg/dL. In other embodiments, the triglyceride levels are reduced from 10 mg/dL to 70 mg/dL; from 20 mg/dL to 60 mg/dL; or

from 30 mg/dL to 50 mg/dL. In one embodiment, the patient has triglyceride levels of 150 mg/dL or higher. In another embodiment, the patient has triglyceride levels of 200 mg/dL or higher. In yet another embodiment, the patient has triglyceride levels of 500 mg/dL or higher.

[027] Provided herein are methods for treating dyslipidemia in patients in need thereof by identifying patients in need of treatment for dyslipidemia and administering to the patients a pharmaceutical formulation comprising a sufficient amount of at least one exendin, exendin agonist or exendin analog agonist to maintain a steady state average, geometric mean, or minimum plasma concentration level of the exendin, exendin agonist, or exendin analog agonist effective to treat dyslipidemia in the patient. "Dyslipidemia" can include one or more of the following: hyperlipidemia (e.g., elevated lipids), hyperglyceridemia (e.g., elevated glycerides), hypertriglyceridemia (e.g., elevated triglycerides), hypercholesterolemia (e.g., elevated cholesterol), hyperlipoproteinemia (e.g., elevated LDL-cholesterol), hyperchylomicronemia (e.g., elevated chylomicrons), and combined hyperlipidemia (e.g., elevated triglycerides and LDL-cholesterol).

[028] Provided herein are methods for treating or slowing the progression of atherosclerosis in patients in need thereof by identifying patients in need of treatment for atherosclerosis and administering to the patients a pharmaceutical formulation comprising a sufficient amount of at least one exendin, exendin agonist or exendin analog agonist to maintain a steady state average, geometric mean, or minimum plasma concentration level of the exendin, exendin agonist, or exendin analog agonist effective to treat or slow the progression of atherosclerosis in the patient. Atherosclerosis is a disease in which plaque builds up on the insides of arteries. The plaque is made up of fat, cholesterol, calcium, and other substances found in blood. Over time, plaque hardens, narrows the arteries, and reduces the flow of oxygen-rich blood to organs and other body parts, which can lead to heart attacks and stroke.

[029] Provided herein are methods for treating, preventing, or reducing the risk of heart attacks and strokes in patients in need thereof by identifying patients in need of treatment, prevention, or risk reduction for heart attacks or strokes and administering to the patients a pharmaceutical formulation comprising a sufficient amount of at least one exendin, exendin agonist or exendin analog agonist to maintain a steady state average, geometric mean, or minimum plasma concentration level of the exendin, exendin agonist, or exendin analog agonist effective to treat, prevent, or reduce the risk of heart attacks or strokes in the patient.

[030] Provided herein are methods of treating diabetes; methods of treating obesity; methods of reducing hemoglobin Ai_{C}; and methods of reducing postprandial blood glucose in patients in need thereof by administering to the patients a pharmaceutical formulation comprising at least one exendin, exendin agonist or exendin analog agonist in an amount sufficient to maintain a steady state geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist of about 145 pg/mL to about 700 pg/mL. In other embodiments, the steady state geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist is about 175 pg/mL to about 650 pg/mL; about 200 pg/mL to about 600 pg/mL; about 200 pg/mL to about 400 pg/mL; or about 300 pg/mL.

[03 1] In some embodiments, the exendin, exendin agonist, or exendin analog agonist is given by chronic administration. "Chronic administration" refers to administration of the formulations containing the exendin, exendin agonist, or exendin analog agonist in a continuous mode (as opposed to an acute mode) to maintain the plasma concentration at or above the level necessary to obtain the desired therapeutic effect for an extended period of time. In one embodiment, the "therapeutically effective amount" is the steady state average plasma concentration (i.e., Css) of the exendin, exendin agonist, or exendin analog agonist. The average plasma concentration is the area under the plasma concentration versus time curve during the dosing interval at steady state divided by the dosing interval. In another embodiment, the "therapeutically effective amount" is the steady state minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist. In yet another embodiment, the "therapeutically effective amount" is the steady state geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist.

[032] The skilled artisan will recognize that the average, geometric mean, or minimum plasma concentration needed to obtain the desired therapeutic effect may not be reached immediately upon administration of the exendin, exendin agonist, or exendin analog agonist, but may take anywhere from hours to days to weeks to be reached. Accordingly, the average, minimum, or geometric mean plasma concentration must be measured at steady state. Once reached, the steady state average, minimum, or geometric mean plasma concentration is maintained for the desired period of time to have its therapeutic effect.

[033] "Chronic administration" also refers to administration of the exendin, exendin agonist, or exendin analog agonist in any manner that achieves the therapeutically effective amount. Exemplary modes of administration include continuous infusion (either intravenously or subcutaneously); the use of a pump or metering system (either implanted or external, for continuous or intermittent delivery); and extended release, slow release,

sustained release or long acting formulations. In one exemplary, the formulation for "chronic administration" is a polymer-based sustained release formulation. Exemplary polymer-based sustained release formulations are described in US Patent No. 6,824,822; US Publication No. 2006/0099271; US Publication No. 2004/0228833; US Publication No. 2004/0208929; US Publication No. 2005/0271702; US Publication No. 2006/01 10423; WO 2004/035754; WO 2004/035762; WO 2004/036186; WO 2005/102293; WO 2005/1 10425; and WO 2007/081321; the disclosures of which are incorporated by reference herein in their entirety. Other exemplary modes of administration include intravenous, transmucosal, intranasal, oral, intramuscular, subcutaneous, transdermal, by inhalation, or by pulmonary administration.

[034] In one embodiment of the formulations and methods described herein, the steady state minimum plasma concentration of the exendin, exendin agonist or exendin analog agonist is at a level of at least about 100 pg/ml, at least about 125 pg/ml, or at least about 145 pg/mL for at least about 1 day, at least about 2 days, at least about 3 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 1 month, at least about 3 months, or at least about 6 months.

[035] In other embodiments of the formulations and methods described herein, the steady state average or minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist is at a level from about 100 pg/ml to about 1,000 pg/ml; from about 100 pg/ml to about 750 pg/ml; from about 145 pg/ml to about 700 pg/ml; from about 150 pg/ml to about 700 pg/ml; from about 150 pg/ml to about 650 pg/ml; from about 200 pg/ml to about 650 pg/ml; from about 200 pg/mL to about 600 pg/mL; or from about 200 pg/mL to about 550 pg/mL. In one embodiment, the plasma concentration is the steady state average plasma concentration.

[036] In still other embodiments of the formulations and methods described herein, the steady state average or minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist is at a level of least about 75 pg/ml, at least about 100 pg/ml, at least about 150 pg/ml, at least about 175 pg/ml, at least about 200 pg/ml, at least about 225 pg/ml, or at least about 250 pg/ml. In one embodiment, the plasma concentration is the steady state average plasma concentration.

[037] In still other embodiments of the formulations and methods described herein, the steady state geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist is at a level from about 145 pg/mL to about 700 pg/mL. In other embodiments, the steady state geometric mean plasma concentration of the exendin, exendin

agonist, or exendin analog agonist is about 175 pg/mL to about 650 pg/mL; about 200 pg/mL to about 600 pg/mL; about 200 pg/mL to about 400 pg/mL; or about 300 pg/mL.

[038] In still other embodiments of the formulations and methods described herein, the steady state average or minimum plasma concentration of the exendin, exendin agonist or exendin analog agonist is greater than 50 pmoles/liter, greater than 60 pmoles/liter, greater than 70 pmoles/liter, greater than 80 pmoles/liter, greater than 90 pmoles/liter, greater than 100 pmoles/liter, greater than 110 pmoles/liter, greater than 120 pmoles/liter, greater than 130 pmoles/liter, greater than 140 pmoles/liter, or greater than 150 pmoles/liter. In one embodiment, the plasma concentration is the steady state average plasma concentration.

[039] In further embodiments of the formulations and methods described herein, any of the above steady state average, geometric mean, or minimum plasma concentrations of at least one exendin, exendin agonist, or exendin analog agonist is maintained for at least one day, at least one week, at least one month, at least three months, or at least one year. In other embodiments of the formulations and methods described herein, any of the above steady state average, geometric mean, or minimum plasma concentrations are maintained for at least about 3 days, at least about 5 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months or at least about one year. In one embodiment of the formulations and methods described herein, the steady state average, geometric mean or minimum plasma concentration is maintained for at least about one week to about twelve weeks; from about one week to about eight weeks; or from about one week to about four weeks.

[040] In any one of the embodiments of the formulations and methods described herein, the circulating plasma exendin, exendin agonist or exendin analog agonist concentrations may be maintained at the steady state average, geometric mean, or minimum plasma concentration or within about 5%, about 10%, about 20%, about 25%, or about 50% of the average, geometric mean, or minimum plasma concentration. In other embodiments, the circulating plasma concentrations are maintained at the average, geometric mean, or minimum given concentration or at about 98%, about 97%, about 96%, about 95%, about 90%, about 80%, about 70%, or about 60% of the average, geometric mean, or minimum concentration.

[041] In one embodiment, the steady state average, geometric mean, or minimum plasma concentration of the exendin, exendin agonist or exendin analog agonist is the steady

state average, geometric mean, or minimum plasma concentration of an exendin, exendin agonist or exendin analog agonist that results in a therapeutic effect (e.g., reduced total cholesterol, LDL-cholesterol, triglycerides) substantially equivalent to that observed with a given steady state average, geometric mean, or minimum plasma concentration of exendin-4. Substantially equivalent may be ±50%, ±25%, ±20%, ±10%, or ±5% to the steady state average, minimum, or geometric mean plasma concentration observed with a given steady state average, minimum, or geometric mean plasma concentration of exendin-4.

[042] Any formulation for sustained release of the exendin, exendin agonist or exendin analog agonist can be used. Exemplary formulations are described in US Patent No. 6,828,303; US Publication Nos. 2006/0084604, 2006/0034923, 2006/0034889 and 2005/0171503; European Patent Application No. 1512395 Al; and WO 2006/041538, WO 2006/017852, WO 2005/041873, WO 2005/112633 and WO 2005/040195, the disclosures of which are incorporated by reference herein in their entirety.

[043] In another embodiment, the exendin, exendin agonist, or exendin analog agonist may be administered in a polymer-based sustained release formulation. Exemplary polymer-based sustained release formulations include the formulations described in US Patent No. 6,824,822; US Publication No. 2006/0099271; US Publication No. 2004/0228833; US Publication No. 2004/0208929; US Publication No. 2005/0271702; US Publication No. 2006/0110423; WO 2004/035754; WO 2004/035762; WO 2004/036186; WO 2005/102293; WO 2005/1 10425; and WO 2007/081321, the disclosures of which are incorporated by reference herein in their entirety.

[044] In some embodiments, the formulations and methods described herein further provide that the exendin, exendin analog or exendin analog agonist is co-administered with one or more cholesterol and/or triglyceride lowering agents. Exemplary agents include HMG CoA reductase inhibitors (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin); bile ace sequestrants (e.g., colesevelam, cholestyramine, colestipol); fibrates (e.g., fenofibrate, clofibrate, gemfibrozil); ezetimibe, nicotinic acid, probucol, a lovastatin/niacin combination; an atorvastatin/amlodipine combination; and a simvastatin/ezetimibe combination. Co-administration can be achieved by separately administering the exendin, exendin agonist, or exendin analog agonist with the cholesterol and/or triglyceride lowering agent, or be administering a single pharmaceutical formulation comprising the exendin, exendin agonist, or exendin analog agonist and the cholesterol and/or triglyceride lowering agent. Appropriate dosage regimens for the cholesterol and/or triglyceride lowering agents are generally known in the art.

[045] The term "exendin" includes naturally occurring (or synthetic versions of naturally occurring) exendin peptides that are found in the salivary secretions of the GiIa monster. Exendins of particular interest include exendin-3 (SEQ ID NO:2) which is present in the salivary secretions of *Heloderma horridum*, and exendin-4 (SEQ ID NO:1) a 39 amino acid peptide which is naturally present in the salivary secretions of *Heloderma suspectum.* Eng et al, *J. Biol. Chem.*, 265:20259-62 (1990); Eng et al, *J. Biol. Chem.*, 267:7402-05 (1992). Exendin-4 as it occurs in the salivary secretions of the GiIa monster is an amidated peptide. It should be appreciated, however, that the exendin agonists and exendin analog agonists for use in the methods described herein are not limited to the amidated forms, but include that acid form, pharmaceutically acceptable salt form, or any other physiologically active form of the molecule. In one embodiment, the term exendin, as it refers to native exendin peptides or synthetic versions of native exendin peptides (e.g., exendin-4, exendin-3), can be used interchangeably with the term "exendin agonist."

[046] "Exendin agonist" and "exendin analog agonist" refer to peptides or other compounds which elicit a biological activity of an exendin reference peptide, preferably having a potency equal to or better than the exendin reference peptide, or within five orders of magnitude (plus or minus) of potency compared to the exendin reference peptide, for example, 4, 3, 2, or 1 orders of magnitude, when evaluated by art-known measures such as receptor binding and/or competition studies as described, e.g., by Hargrove et al, *Regulatory Peptides*, 141:1 13-1 19 (2007), the disclosure of which is incorporated by reference herein. In one embodiment, the term refers to a peptide or compound which elicits a biological effect similar to that of the exendin reference peptide, for example a compound (1) having activity in cholesterol lowering assays similar to the exendin reference peptide, and (2) which optionally binds specifically in a reference receptor assay or in a competitive binding assay with labeled exendin reference peptide. Preferably, the exendin agonists will bind in such assays with an affinity of less than 1 μM, and more preferably with an affinity of less than 1-5 nM. Such exendin agonists may comprise a polypeptide comprising an active fragment of a reference peptide or a small chemical molecule. In one embodiment, the exendin agonist is a peptide, preferably exendin-4. Exendin agonists and exendin analog agonists do not include GLP-I and variants, analogs and derivatives thereof.

[047] The term "pharmaceutically acceptable carrier" refers to a non-toxic compound that may be administered to a patient together with an exendin agonist or exendin analog agonist of the invention, and which does not destroy the pharmacological activity thereof. Pharmaceutically acceptable carriers include any and all solvents, dispersion media,

coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

[048] Exendin sequences compared to the sequence of GLP-I are: H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R-NH_2 (GLP- 1(7-3 O)-NH_2 (SEQ ID NO:3); H S D G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S-NH_2 (exendin-3-NH_2 (SEQ ID NO:2)); D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S-NH_2 (exendin-4(9-39)-NH_2 (SEQ ID NO:4)); H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S-NH_2 (exendin-4-NH_2 (SEQ ID NO:1)); H S D A T F T A E Y S K L L A K L A L Q K Y L E S I L G S S T S P R P P S S (helospectin I (SEQ ID NO:5)); H S D A T F T A E Y S K L L A K L A L Q K Y L E S I L G S S T S P R P P S (helospectin II (SEQ ID NO:6)); H S D A I F T E E Y S K L L A K L A L Q K Y L A S I L G S R T S P P P-NH_2 (helodermin-NH_2 (SEQ ID NO:7)): and H S D A I F T Q Q Y S K L L A K L A L Q K Y L A S I L G S R T S P P P-NH_2 (Q^8,Q^9 helodermin-NH_2 (SEQ ID NO:8)).

[049] The structure activity relationship of exendin was investigated for structures that may relate to the activity of exendin, for its stability to metabolism, and for improvement of its physical characteristics, especially as it pertains to peptide stability and to amenability to alternative delivery systems, and various exendin analog agonist peptide compounds have been developed. Exendin analog agonists include exendin analogs with agonist activity in which one or more naturally occurring amino acids are inserted, eliminated or replaced with another amino acid(s). Exemplary exendin analog agonists are peptide analogs of exendin-4. In one aspect, the methods of reducing total cholesterol levels, reducing LDL-cholesterol levels, reducing triglyceride levels, and treating dyslipidemia comprise the chronic administration of an exendin analog agonist to a patient in need thereof.

[050] Exendin analog agonists include peptides that are encoded by polynucleotides that express biologically active exendin analogs with agonist activity, as defined herein. For instance, exendin analog agonists may be peptides containing one or more amino acid substitutions, additions or deletions, compared with reference exendin, for example, exendin-4. In one embodiment, the number of substitutions, deletions, or additions is 15 amino acids or less, 10 amino acids or less, 5 amino acids or less, 3 amino acids or less, 2 amino acids or less, or 1 amino acid or less. In one aspect of the invention, the substitutions include one or

more conservative substitutions. A "conservative" substitution denotes the replacement of an amino acid residue by another, biologically active, similar residue. Examples of conservative substitutions include the substitution of one hydrophobic residue, such as isoleucine, valine, leucine, or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. The following table lists illustrative, but non-limiting, conservative amino acid substitutions.

TABLE

ORIGINAL RESIDUE	EXEMPLARY SUBSTITUTIONS
ALA	SER, THR
ARG	LYS
ASN	HIS, SER
ASP	GLU, ASN
CYS	SER
GLN	ASN, HIS
GLU	ASP
GLY	ALA, SER
HIS	ASN, GLN
ILE	LEU, VAL, THR
LEU	ILE, VAL
LYS	ARG, GLN, GLU, THR
MET	LEU, ILE, VAL
PHE	LEU, TYR
SER	THR, ALA, ASN
THR	SER, ALA
TRP	ARG, SER
TYR	PHE
VAL	ILE, LEU, ALA
PRO	ALA

[05 1] It is further understood that exendin analog agonists include the peptides described herein which have been chemically derivatized or altered, for example, peptides with non-natural amino acid residues (e.g., taurine, β-amino acid residues, γ-amino acid residues, and D-amino acid residues), C-terminal functional group modifications, such as amides, esters, and C-terminal ketone modifications and N-terminal functional group modifications, such as acylated amines, Schiff bases, or cyclization, as found, for example, in the amino acid pyroglutamic acid.

[052] Such derivatized peptides include exendins, exendin agonists and exendin analog agonists conjugated (with or without a linking group) to one or more polymer molecules, such as polyethylene glycol ("PEG"), albumin, fatty acid chains of various lengths *(e.g.,* stearyl, palmitoyl, octanoyl, etc.), or by the addition of polyamino acids, such as poly-his, poly-arg, poly-lys, and poly-ala. Modifications to the exendins, exendin agonists and exendin analog agonists can also include small molecule substituents, such as short alkyls and constrained alkyls *(e.g.,* branched, cyclic, fused, adamantyl), and aromatic groups. The polymer molecules will typically have a molecular weight ranging from about 500 to about 20,000 Daltons. Albumin has a molecular weight of about 67,000 Daltons. Such peptides are described, for example, in US Patent No. 6,924,264, and 6,593,295, the disclosure of which are incorporated by reference herein in their entirety. Exemplary modified peptides include $(His)_x$-[Exendin-4(l-39)]-$(Lys)_y$ where x is 0, 1 or 2; and y is an integer from 2-8; and [Exendin-4(1-39)]-(linking group)-albumin, where the linking group comprises (i) one or more Lys amino acids adjacent the C-terminal end of the exendin 4, (ii) a maleimide group, (iii) a -$(OCH_2CH_2)_Z$- group where z is 1, 2, 3, or 4; or (iv) a combination thereof.

[053] Such polymer-conjugations and small molecule substituent modifications may occur singularly at the N- or C-terminus or at the side chains of amino acid residues within the sequence of the polypeptides. Alternatively, there may be multiple sites of derivatization along the hybrid polypeptide. Substitution of one or more amino acids with lysine, aspartic acid, glutamic acid, or cysteine may provide additional sites for derivatization. See, e.g., U.S. Patent Nos. 5,824,784 and 5,824,778. In one embodiment, the polypeptides may be conjugated to one, two, or three polymer molecules.

[054] The polymer molecules may be linked to an amino, carboxyl, or thiol group, and may be linked by N or C terminus, or at the side chains of lysine, aspartic acid, glutamic acid, or cysteine. Alternatively, the polymer molecules may be linked with diamine and dicarboxylic groups. In one embodiment, the polypeptides are conjugated to one, two, or three PEG molecules through an epsilon amino group on a lysine amino acid.

[055] Also included in the invention are exendin analog sequences having 80% sequence identity, 90% sequence identity, 95% sequence identity, or 99% sequence identity to a reference exendin peptide, for example, (1) SEQ ID NO:1; (2) SEQ ID NO:2; or (2) truncated sequences of SEQ ID NO: 1 or SEQ ID NO:2, wherein the truncated sequences contain at least 10 amino acids, at least 20 amino acids, at least 25 amino acids, at least 30 amino acids, at least 35 amino acids, at least 38 amino acids or N-I amino acids where N equals the number of amino acids in the full length or reference peptide or protein. As used

herein, sequence identity refers to a comparison made between two molecules using standard algorithms well known in the art. In one embodiment, the algorithm for calculating sequence identity for the invention is the Smith-Waterman algorithm, where an exendin, for example SEQ ID NO:1 (i.e., exendin-4), is used as the reference sequence to define the percentage identity of a comparison peptide over its length. The choice of parameter values for matches, mismatches, and insertions or deletions is discretionary, although some parameter values have been found to yield more biologically realistic results than others. In one embodiment, the set of parameter values for the Smith-Waterman algorithm is set forth in the "maximum similarity segments" approach, which uses values of 1 for a matched residue and -¼ for a mismatched residue (a residue being either a single nucleotide or single amino acid). Waterman, *Bull. Math. Biol.* 46; 473 (1984). Insertions and deletions (indels), x, are weighted as $x_k = 1 + ¼k$, where k is the number of residues in a given insertion or deletion. *Id.*

[056] Other exendins, exendin agonists, and exendin analog agonists useful in the invention include those described in WO 98/05351; WO 99/07404; WO 99/25727; WO 99/25728; WO 99/40788; WO 00/41546; WO 00/41548; WO 00/73331; WO 01/51078; WO 03/099314; US Patent No. 6,956,026; US Patent No. 6,506,724; US Patent No. 6,703,359; US Patent No. 6,858,576; US Patent No. 6,872,700; US Patent No. 6,902,744; US Patent No. 7,157,555; US Patent No. 7,223,725; US Patent No. 7,220,721; US Publication No. 2003/0036504; and US Publication No. 2006/0094652, the disclosures of which are incorporated by reference herein in their entirety.

[057] Certain exemplary exendins, exendin agonists, and exendin analog agonists include: exendin-4 (1-30) (SEQ ID NO:9: His GIy GIu GIy Thr Phe Thr Ser Asp Leu Ser Lys GIn Met GIu GIu GIu Ala VaI Arg Leu Phe He GIu Trp Leu Lys Asn GIy GIy); exendin-4 (1-30) amide (SEQ ID NO: 10: His GIy GIu GIy Thr Phe Thr Ser Asp Leu Ser Lys GIn Met GIu GIu GIu Ala VaI Arg Leu Phe He GIu Trp Leu Lys Asn GIy GIy-NH_2); exendin-4 (1-28) amide (SEQ ID NO: 11: His GIy GIu GIy Thr Phe Thr Ser Asp Leu Ser Lys GIn Met GIu GIu GIu Ala VaI Arg Leu Phe He GIu Trp Leu Lys Asn-NH_2); ^{14}Leu,^{25}Phe exendin-4 amide (SEQ ID NO: 12: His GIy GIu GIy Thr Phe Thr Ser Asp Leu Ser Lys GIn Leu GIu GIu GIu Ala VaI Arg Leu Phe He GIu Phe Leu Lys Asn GIy GIy Pro Ser Ser GIy Ala Pro Pro Pro Ser-NH_2); ^{14}Leu,^{25}Phe exendin-4 (1-28) amide (SEQ ID NO: 13: His GIy GIu GIy Thr Phe Thr Ser Asp Leu Ser Lys GIn Leu GIu GIu GIu Ala VaI Arg Leu Phe He GIu Phe Leu Lys Asn-NH_2); and ^{14}Leu,^{22}Ala,^{25}Phe exendin-4 (1-28) amide (SEQ ID NO: 14: His GIy GIu GIy Thr Phe Thr Ser Asp Leu Ser Lys GIn Leu GIu GIu GIu Ala VaI Arg Leu Ala He GIu Phe Leu Lys Asn-NH_2).

[058] Exendin analog agonists for use in the formulations and methods described herein also include those described in U S Patent No. 7,223,725, such as compounds of formula (I) (SEQ ID NO: 15) or a pharmaceutically acceptable salt thereof: Xaai Xaa$_{2}$ Xaa$_{3}$ GIy Xaa$_{5}$ Xaa$_{6}$ Xaa$_{7}$ Xaa$_{8}$ Xaa$_{9}$ Xaaio Xaa π Xaai$_{2}$ Xaai3 Xaa$_{14}$ Xaai$_{5}$ Xaai$_{6}$ Xaa$_{17}$ Ala Xaa$_{19}$ Xaa$_{2}$oXaa$_{2}$i Xaa$_{22}$ Xaa$_{2}$3 Xaa$_{24}$ Xaa$_{2}$5 Xaa$_{2}$6 Xaa$_{2}$7 Xaa$_{2}$8-Zi; wherein Xaai is His, Arg or Tyr; Xaa$_{2}$ is Ser, GIy, Ala or Thr; Xaa3 is Ala, Asp or GIu; Xaas is Ala or Thr; Xaa$_{6}$ is Ala, Phe, Tyr or naphthylalanine; Xaa$_{7}$ is Thr or Ser; Xaa$_{8}$ is Ala, Ser or Thr; Xaa$_{9}$ is Asp or GIu; Xaaio is Ala, Leu, He, VaI, pentylglycine or Met; Xaan is Ala or Ser; Xaai$_{2}$ is Ala or Lys; Xaai3 is Ala or GIn; Xaa$_{14}$ is Ala, Leu, He, pentylglycine, VaI or Met; Xaais is Ala or GIu; Xaai$_{6}$ is Ala or GIu; Xaa$_{17}$ is Ala or GIu; Xaaig is Ala or VaI; Xaa$_{2}$o is Ala or Arg; Xaa$_{2}$i is Ala or Leu; Xaa$_{22}$ is Ala, Phe, Tyr or naphthylalanine; Xaa$_{2}$3 is He, VaI, Leu, pentylglycine, tert-butylglycine or Met; Xaa24 is Ala, GIu or Asp; Xaa25 is Ala, Trp, Phe, Tyr or naphthylalanine; Xaa$_{2}$6 is Ala or Leu; Xaa$_{2}$7 is Ala or Lys; Xaa$_{2}$8 is Ala or Asn; Zi is -OH, -NH$_{2}$, Gly-Z$_{2}$, GIy GIy-Z$_{2}$, GIy GIy Xaa$_{3}$i-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy AIa-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy Ala Xaa$_{36}$-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy Ala Xaa$_{36}$ Xaa$_{37}$-Z$_{2}$ or GIy GIy Xaa$_{31}$ Ser Ser GIy Ala Xaa$_{36}$ Xaa$_{37}$ Xaa38-Z$_{2}$; Xaa3i, Xaa36, Xaa37 and Xaa38 are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; and Z$_{2}$ is -OH or -NH$_{2}$; provided that no more than three of Xaa3, Xaas, Xaa$_{6}$, Xaas, Xaaio, Xaan, Xaai$_{2}$, Xaa$_{13}$, Xaai$_{4}$, Xaais, Xaai$_{6}$, Xaa$_{17}$, Xaai$_{9}$, Xaa$_{20}$, Xaa$_{2}$i, Xaa$_{24}$, Xaa$_{25}$, Xaa$_{26}$, Xaa$_{27}$ and Xaa$_{28}$ are Ala.

[059] Exemplary N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups, for example, of 1 to about 6 carbon atoms, or of 1 to 4 carbon atoms. Exemplary exendin analogs include those wherein Xaai is His or Tyr. More preferably Xaai is His. Provided are those compounds wherein Xaa$_{2}$ is GIy. Provided are those compounds wherein Xaai$_{4}$ is Leu, pentylglycine or Met. Exemplary compounds are those wherein Xaa$_{25}$ is Trp or Phe. Exemplary compounds are those where Xaa$_{6}$ is Phe or naphthylalanine; Xaa$_{22}$ is Phe or naphthylalanine and Xaa$_{23}$ is He or VaI. Provided are compounds wherein Xaa3i, Xaa36, Xaa37 and Xaa38 are independently selected from Pro, homoproline, thioproline and N-alkylalanine. Preferably Zi is -NH$_{2}$. Preferably Z$_{2}$ is -NH$_{2}$.

[060] According to one embodiment, provided are compounds of formula (I) wherein Xaai is His or Tyr, more preferably His; Xaa$_{2}$ is GIy; Xaa6 is Phe or naphthylalanine; Xaai$_{4}$ is Leu, pentylglycine or Met; Xaa$_{22}$ is Phe or naphthylalanine; Xaa$_{2}$3 is He or VaI;

Xaa3i, Xaa36, Xaa37 and Xaa3$_{8}$ are independently selected from Pro, homoproline, thioproline or N-alkylalanine. More preferably Zi is -NH$_{2}$.

[061] According to one embodiment, exemplary compounds include those of formula (I) wherein: Xaai is His or Arg; Xaa$_{2}$ is GIy or Ala; Xaa$_{3}$ is Asp or GIu; Xaa$_{5}$ is Ala or Thr; Xaa$_{6}$ is Ala, Phe or naphthylalanine; Xaa$_{7}$ is Thr or Ser; Xaa$_{8}$ is Ala, Ser or Thr; Xaa$_{9}$ is Asp or GIu; Xaaio is Ala, Leu or pentylglycine; Xaan is Ala or Ser; Xaai$_{2}$ is Ala or Lys; Xaai3 is Ala or GIn; Xaa$_{14}$ is Ala, Leu or pentylglycine; Xaais is Ala or GIu; Xaai$_{6}$ is Ala or GIu; Xaan is Ala or GIu; Xaai$_{9}$ is Ala or VaI; Xaa$_{2}$o is Ala or Arg; Xaa$_{2}$i is Ala or Leu; Xaa$_{22}$ is Phe or naphthylalanine; Xaa$_{23}$ is He, VaI or tert-butylglycine; Xaa$_{24}$ is Ala, GIu or Asp; Xaa$_{25}$ is Ala, Trp or Phe; Xaa$_{26}$ is Ala or Leu; Xaa$_{27}$ is Ala or Lys; Xaa$_{28}$ is Ala or Asn; Zi is -OH, -NH$_{2}$, GIy-Z$_{2}$, GIy GIy-Z$_{2}$, GIy GIy Xaa$_{3}$i-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser-Z$_{2}$, GIy GIy Xaa$_{3}$i Ser Ser GIy-Z$_{2}$, GIy GIy Xaa$_{3}$i Ser Ser GIy AIa-Z$_{2}$, GIy GIy Xaa$_{3}$i Ser Ser GIy Ala Xaa$_{36}$-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy Ala Xaa$_{36}$ Xaa$_{37}$-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy Ala Xaa$_{36}$ Xaa$_{37}$ Xaa$_{38}$-Z$_{2}$; Xaa$_{3}$i, Xaa$_{36}$, Xaa$_{37}$ and Xaa$_{38}$ being independently Pro homoproline, thioproline or N-methylalanine; and Z$_{2}$ being -OH or -NH$_{2}$; provided that no more than three of Xaa$_{3}$, Xaa$_{5}$, Xaa$_{6}$, Xaa$_{8}$, Xaaio, Xaan, Xaai$_{2}$, Xaai$_{3}$, Xaai$_{4}$, Xaai$_{5}$, Xaai$_{6}$, Xaan, Xaaig, Xaa$_{2}$o, Xaa$_{2}$i, Xaa$_{24}$, Xaa$_{25}$, Xaa$_{26}$, Xaa$_{27}$ and Xaa$_{28}$ are Ala. Other exemplary compounds include those set forth in WO 99/25727 identified therein as compounds 2-23.

[062] According to another embodiment, provided are compounds where Xaai$_{4}$ is Leu, He, VaI or pentylglycine, more preferably Leu or pentylglycine, and Xaa$_{25}$ is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will be less susceptive to oxidative degradation, both in vitro and in vivo, as well as during synthesis of the compound.

[063] Exendin analog agonists for use in the formulations and methods described herein also include those described in US Patent No. 7,220,721, such as compounds of formula (II) (SEQ ID NO: 16) or a pharmaceutically acceptable salt thereof: Xaai Xaa$_{2}$ Xaa$_{3}$ Xaa$_{4}$ Xaa$_{5}$ Xaa$_{6}$ Xaa$_{7}$ Xaa$_{8}$ Xaa$_{9}$ Xaaio Xaan Xaai$_{2}$ Xaai3 Xaa$_{14}$ Xaai$_{5}$ Xaai$_{6}$ Xaan Ala Xaai$_{9}$ Xaa$_{20}$ Xaa$_{2}$i Xaa$_{22}$ Xaa$_{23}$ Xaa$_{24}$ Xaa$_{25}$ Xaa$_{26}$ Xaa$_{27}$ Xaa$_{28}$-Zi; wherein: Xaai is His, Arg, Tyr, Ala, Norval, VaI or Norleu; Xaa$_{2}$ is Ser, GIy, Ala or Thr; Xaa$_{3}$ is Ala, Asp or GIu; Xaa$_{4}$ is Ala, Norval, VaI, Norleu or GIy; Xaa$_{5}$ is Ala or Thr; Xaa$_{6}$ is Ala, Phe, Tyr or naphthylalanine; Xaa$_{7}$ is Thr or Ser; Xaa$_{8}$ is Ala, Ser or Thr; Xaa$_{9}$ is Ala, Norval, VaI, Norleu, Asp or GIu; Xaaio is Ala, Leu, He, VaI, pentylglycine or Met; Xaan is Ala or Ser; Xaai$_{2}$ is Ala or Lys; Xaai$_{3}$ is Ala or GIn; Xaai$_{4}$ is Ala, Leu, He, pentylglycine, VaI or Met; Xaais is Ala or GIu; Xaai6 is Ala or GIu; Xaan is Ala or GIu; Xaai$_{9}$ is Ala or VaI; Xaa$_{2}$o is

Ala or Arg; Xaa_2i is Ala or Leu; Xaa_{22} is Phe, Tyr or naphthyl-alanine; $Xaa_2$3 is He, VaI, Leu, pentylglycine, tert-butylglycine or Met; Xaa_{24} is Ala, GIu or Asp; $Xaa_2$5 is Ala, Trp, Phe, Tyr or naphthylalanine; $Xaa_2$6 is Ala or Leu; $Xaa_2$7 is Ala or Lys; $Xaa_2$8 is Ala or Asn; Zi is -OH, -NH_2, GIy-Z_2, GIy GIy-Z_2, GIy GIy Xaa_3i-Z_2, GIy GIy Xaa_{31} Ser-Z_2, GIy GIy Xaa_{31} Ser Ser-Z_2, GIy GIy Xaa_{31} Ser Ser GIy-Z_2, GIy GIy Xaa_{31} Ser Ser GIy AIa-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2 or GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38} Xaa_{39}-Z_2; Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa_{39} is Ser or Tyr; and Z_2 is -OH or -NH_2; provided that no more than three of Xaa_3, Xaa_4, Xaas, Xaa_6, Xaa_8, Xaag, Xaaio, Xaan, $Xaai_2$, $Xaai_3$, $Xaai_4$, $Xaai_5$, $Xaai_6$, Xaan, $Xaai_9$, Xaa_{20}, Xaa_2i, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala; and provided also that, if Xaai is His, Arg or Tyr, then at least one of Xaa_3, Xaa_4 and Xaa_9 is Ala.

[064] Exemplary N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups, for example, of 1 to about 6 carbon atoms, or of 1 to 4 carbon atoms. In one embodiment, such exendin analogs include those wherein Xaai is His, Ala or Norval. More preferably Xaai is His or Ala. Most preferably Xaai is His. Provided are those compounds of formula (II) wherein Xaa_2 is GIy. Provided are those compounds of formula (II) wherein Xaa_3 is Ala. Provided are those compounds of formula (II) wherein Xaa_4 is Ala. Provided are those compounds of formula (II) wherein Xaa_9 is Ala. Provided are those compounds of formula (II) wherein $Xaai_4$ is Leu, pentylglycine or Met. Exemplary compounds of formula (II) are those wherein Xaa_{25} is Trp or Phe. Exemplary compounds of formula (II) are those where Xaa_6 is Ala, Phe or naphthylalanine; Xaa_{22} is Phe or naphthylalanine; and Xaa_{23} is He or VaI. Provided are compounds of formula (II) wherein Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from Pro, homoproline, thioproline and N-alkylalanine. Preferably Zi is -NH_2. Preferably Z_2 is -NH_2.

[065] According to one embodiment, provided are compounds of formula (II) wherein Xaai is Ala, His or Tyr, more preferably Ala or His; Xaa_2 is Ala or GIy; Xaa_6 is Phe or naphthylalanine; $Xaai_4$ is Ala, Leu, pentylglycine or Met; Xaa_{22} is Phe or naphthylalanine; Xaa_{23} is He or VaI; Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from Pro, homoproline, thioproline or N-alkylalanine; and Xaa_{39} is Ser or Tyr, more preferably Ser. More preferably Zi is -NH_2.

[066] According to another embodiment, exemplary compounds include those of formula (II) wherein: Xaai is His or Ala; Xaa_2 is GIy or Ala; Xaa_3 is Ala, Asp or GIu; Xaa_4 is

Ala or GIy; Xaas is Ala or Thr; Xaa_6 is Phe or naphthylalanine; Xaa7 is Thr or Ser; Xaa_8 is Ala, Ser or Thr; Xaa_9 is Ala, Asp or GIu; Xaaio is Ala, Leu or pentylglycine; Xaan is Ala or Ser; Xaa_{12} is Ala or Lys; Xaa_{13} is Ala or GIn; $Xaai_4$ is Ala, Leu, Met or pentylglycine; Xaais is Ala or GIu; $Xaai_6$ is Ala or GIu; Xaan is Ala or GIu; $Xaai_9$ is Ala or VaI; Xaa_2o is Ala or Arg; Xaa_2i is Ala or Leu; Xaa_{22} is Phe or naphthylalanine; Xaa_23 is He, VaI or tert-butylglycine; Xaa_{24} is Ala, GIu or Asp; Xaa_25 is Ala, Trp or Phe; Xaa_26 is Ala or Leu; Xaa_27 is Ala or Lys; Xaa_{28} is Ala or Asn; Z_x is -OH, $-NH_2$, GIy-Z_2, GIy GIy-Z_2, GIy GIy Xaa_3i-Z_2, GIy GIy Xaa_{31} Ser-Z_2, GIy GIy Xaa_{31} Ser Ser-Z_2, GIy GIy Xaa_{31} Ser Ser GIy-Z_2, GIy GIy Xaa_{31} Ser Ser GIy AIa-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37}-Z_2, GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2 or GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38} Xaa_{39}-Z_2; Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} being independently Pro homoproline, thioproline or N-methylalanine; and Z_2 being -OH or $-NH_2$; provided that no more than three of Xaa_3, Xaas, Xaa_6, Xaas, Xaaio, Xaan, $Xaai_2$, $Xaai_3$, $Xaai_4$, Xaais, Xaai6, Xaan, $Xaai_9$, Xaa_{20}, Xaa_2i, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala; and provided also that, if Xaai is His, Arg or Tyr, then at least one of Xaa_3, Xaa_4 and Xaa_9 is Ala.

[067] According to still another embodiment, provided are compounds of formula (II) where $Xaai_4$ is Ala, Leu, He, VaI or pentylglycine, more preferably Leu or pentylglycine, and Xaa_{25} is Ala, Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will be less susceptible to oxidative degradation, both *in vitro* and *in vivo*, as well as during synthesis of the compound.

[068] Exemplary compounds of formula (II) include those described in WO 99/25728 as having the amino acid sequence of SEQ ID NOs: 5-93 therein which are hereby incorporated by reference.

[069] In other embodiments of the formulations and methods described herein, the exendin analog includes narrower genera of US Patent No. 7,223,725, having formula (III) (SEQ ID NO: 17) or a pharmaceutically acceptable salt thereof: Xaai Xaa_2 Xaa_3 GIy Xaas Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaaio Xaan $Xaai_2$ $Xaai_3$ Xaa_{14} $Xaai_5$ $Xaai_6$ Xaan Ala $Xaai_9$ Xaa_{20} Xaa_2i Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Zi; wherein: Xaai is His or Arg; Xaa_2 is GIy or Ala; Xaa_3 is Ala, Asp or GIu; Xaas is Ala or Thr; Xaa_6 is Ala, Phe or naphthylalanine; Xaa_7 is Thr or Ser; Xaa_8 is Ala, Ser or Thr; Xaa_9 is Asp or GIu; Xaaio is Ala, Leu or pentylglycine; Xaan is Ala or Ser; $Xaai_2$ is Ala or Lys; $Xaai_3$ is Ala or GIn; $Xaai_4$ is Ala, Leu or pentylglycine; Xaais is Ala or GIu; $Xaai_6$ is Ala or GIu; Xaan is Ala or GIu; Xaa_{19} is Ala or VaI; Xaa_2o is Ala or Arg; Xaa_2i is Ala or Leu; Xaa_{22} is Phe or naphthylalanine; Xaa_{23} is He, VaI or tert-butylglycine; Xaa_{24} is Ala, GIu or Asp; Xaa_{25} is Ala, Trp, or Phe; Xaa_26 is Ala or

Leu; Xaa_{27} is Ala or Lys; Xaa_{28} is Ala or Asn; Z_1 is -OH, -NH_2, GIy-Z_2, GIy GIy -Z_2, GIy GIy Xaa_3i-Z_2, GIy GIy Xaa_{31} Ser-Z_2, GIy GIy Xaa_{31} Ser Ser-Z_2, GIy GIy Xaa_{31} Ser Ser GIy-Z_2, GIy GIy Xaa_{31} Ser Ser GIy AIa-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37}-Z_2 or GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2; Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from the group consisting of Pro, homoproline, thioproline and N-methylalanine; and Z_2 is -OH or -NH_2; provided that no more than three of Xaa_3, Xaa_5, Xaa_6, Xaa_8, Xaaio, Xaan, Xaai $_2$, Xaai $_3$, Xaai $_4$, Xaai $_5$, Xaai $_6$, Xaan, Xaaig, Xaa_{2}o, Xaa_2i, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala; and pharmaceutically acceptable salts thereof.

[070] In other embodiments of the formulations and methods described herein, the exendin analog includes narrower genera of compounds described in US Patent No. 7,220,721, having formula (IV) (SEQ ID NO:18) or a pharmaceutically acceptable salt thereof: Xaai Xaa_2 Xaa_3 Xaa_4 Xaas Xaa_6 Xaa_7 Xaa_8 Xaag Xaaio Xaan Xaai $_2$ Xaai $_3$ Xaai $_4$ Xaais Xaai $_6$ Xaan Ala Xaai $_9$ Xaa_{20} Xaa_2i Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Zi; wherein: Xaai is His or Ala; Xaa_2 is GIy or Ala; Xaa_3 is Ala, Asp or GIu; Xaa_4 is Ala or GIy; Xaa_5 is Ala or Thr; Xaa_6 is Ala, Phe or naphthylalanine; Xaa_7 is Thr or Ser; Xaa_8 is Ala, Ser or Thr; Xaa_9 is Ala, Asp or GIu; Xaaio is Ala, Leu or pentylglycine; Xaan is Ala or Ser; Xaai $_2$ is Ala or Lys; Xaai $_3$ is Ala or GIn; Xaa_{14} is Ala, Leu, Met or pentylglycine; Xaai $_5$ is Ala or GIu; Xaai6 is Ala or GIu; Xaan is Ala or GIu; Xaa_{19} is Ala or VaI; Xaa_2o is Ala or Arg; Xaa_2i is Ala or Leu; Xaa_{22} is Phe or naphthyl-alanine; Xaa_{23} is He, VaI or tert-butylglycine; Xaa_{24} is Ala, GIu or Asp; $Xaa_2$5 is Ala, Trp or Phe; $Xaa_2$6 is Ala or Leu; Xaa_{27} is Ala or Lys; Xaa_{28} is Ala or Asn; Z_1 is -OH, -NH_2, GIy-Z_2, GIy GIy-Z_2, GIy GIy Xaa_{31}-Z_2, GIy GIy Xaa_{31} Ser-Z_2, GIy GIy Xaa_{31} Ser Ser-Z_2, GIy GIy Xaa_{31} Ser Ser GIy-Z_2, GIy GIy Xaa_{31} Ser Ser GIy AIa-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala $Xaa_3$6 Xaa_{37} Xaa_{38} Ser-Z_2; Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently Pro, homoproline, thioproline, or N-methylalanine; and Z_2 is -OH or -NH_2; provided that no more than three of Xaa_3, Xaa_5, Xaa_6, Xaa_8, Xaaio, Xaan, Xaai $_2$, Xaai $_3$, Xaai $_4$, Xaai $_5$, Xaai $_6$, Xaan, Xaaig, Xaa_{2}o, Xaa_2i, Xaa_{24}, $Xaa_2$5, $Xaa_2$6, Xaa_{27}, and Xaa_{28} are Ala; and provided that, if Xaai is His, Arg or Tyr, then at least one of Xaa_3, Xaa_4 and Xaa_9 is Ala; and pharmaceutically acceptable salts thereof.

[071] Exemplary compounds of formula (IV) include those wherein Xaai is His or Ala. Preferably, Xaai is His. Exemplary compounds of formula (IV) include those wherein Xaa_2 is GIy. Exemplary compounds of formula (IV) include those wherein Xaa4 is Ala.

Exemplary compounds of formula (IV) include those wherein Xaa_9 is Ala. Exemplary compounds of formula (IV) include those wherein Xaa_{14} is Leu, pentylglycine or Met. Exemplary compounds of formula (IV) include those wherein $Xaa_2$5is Trp or Phe. Exemplary compounds of formula (IV) include those wherein Xaa_6 is Ala, Phe or naphthylalanine; Xaa_{22} is Phe or naphthylalanine; and $Xaa_2$3is He or VaI. Exemplary compounds of formula (IV) include those wherein Zi is $-NH_2$. Exemplary compounds of formula (IV) include those wherein Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine. Exemplary compounds of formula (IV) include those wherein Z_2 is $-NH_2$. Exemplary compounds of formula (IV) include those wherein Zi is $-NH_2$.

[072] Also provided are compounds for use in the formulations and methods described herein are those described in US Patent No. 7,223,725, including compounds of formula (V) (SEQ ID NO: 19) or a pharmaceutically acceptable salt thereof: Xaai Xaa_2 Xaa_3 GIy Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaaio Xaaπ $Xaai_2$ $Xaai_3$ Xaa_{14} $Xaai_5$ $Xaai_6$ Xaa_{17} Ala Xaa_{19} Xaa_2o Xaa_2i Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Zi; wherein Xaai is His, Arg or Tyr or 4-imidazo-propionyl; Xaa_2 is Ser, GIy, Ala or Thr; Xaa_3 is Ala, Asp or GIu; Xaa_5 is Ala or Thr; Xaa_6 is Ala, Phe, Tyr or naphthylalanine; Xaa_7 is Thr or Ser; Xaa_8 is Ala, Ser or Thr; Xaa_9 is Asp or GIu; Xaaio is Ala, Leu, He, VaI, pentylglycine or Met; Xaaπ is Ala or Ser; $Xaai_2$ is Ala or Lys; $Xaai_3$ is Ala or GIn; $Xaai_4$ is Ala, Leu, He, pentylglycine, VaI or Met; Xaais is Ala or GIu; $Xaai_6$ is Ala or GIu; Xaa_{17} is Ala or GIu; $Xaai_9$ is Ala or VaI; Xaa_{20} is Ala or Arg; Xaa_2i is Ala, Leu or Lys-NH^{ε}-R where R is Lys, Arg, C_1-C_{10} straight chain or branched alkanoyl or cycloalkylalkanoyl; Xaa_{22} is Phe, Tyr or naphthylalanine; Xaa_{23} is He, VaI, Leu, pentylglycine, tert-butylglycine or Met; Xaa_{24} is Ala, GIu or Asp; Xaa_{25} is Ala, Trp, Phe, Tyr or naphthylalanine; Xaa_{26} is Ala or Leu; Xaa_{27} is Lys, Asn, Ala or Lys-NH^{ε}-R where R is Lys, Arg, Ci-Ci_0 straight chain or branched alkanoyl or cycloalkylalkanoyl; X_{28} is Lys, Asn, Ala or Lys-NH^{ε}-R where R is Lys, Arg, Ci-Ci_0 straight chain or branched alkanoyl or cycloalkylalkanoyl; Z_1 is -OH, $-NH_2$, GIy-Z_2, GIy GIy-Z_2, GIy GIy Xaa_{31}-Z_2, GIy GIy Xaa_{31} Ser-Z_2, GIy GIy Xaa_{31} Ser Ser-Z_2, GIy GIy Xaa_{31} Ser Ser GIy-Z_2, GIy GIy Xaa_{31} Ser Ser GIy AIa-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37}-Z_2 or GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2; Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine and N-alkylalanine; and Z_2 is -OH

or $-NH_2$; provided that no more than three of Xaa3, Xaas, Xaa_6, Xaas, Xaaio, Xaan, $Xaai_2$, Xaai3, $Xaai_4$, $Xaai_5$, $Xaai_6$, Xaan, $Xaai_9$, Xaa_{2o}, Xaa_2i, Xaa_{24}, Xaa_{25}, and Xaa_{26} are Ala.

[073] Exemplary exendin analogs of formula (V) include those wherein Xaai is His, Tyr or 4-imidazopropionyl. More preferably Xaai is His. Provided are those compounds of formula (V) wherein Xaai is 4-imidazopropionyl. Provided are those compounds of formula (V) wherein Xaa_2 is GIy. Exemplary compounds of formula (V) are those wherein $Xaai_4$ is Leu, pentylglycine or Met. Exemplary compounds of formula (V) are those wherein Xaa_{25} is Trp or Phe.

[074] According to one embodiment, provided are compounds of formula (V) wherein Xaa_6 is Phe or naphthylalanine; and Xaa_{22} is Phe or naphthylalanine; and Xaa_23 is He or VaI. More preferably, Zi is $-NH_2$. According to one embodiment, provided are compounds of formula (V) wherein Xaa3i, Xaa36, Xaa37 and Xaa38 are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine. Preferably, Z_2 is $-NH_2$. Exemplary compounds of formula (V) include those wherein X_{27} is Lys or Lys-NH^{ε}-R where R is Lys, Arg, C_1-C_{10} straight chain or branched alkanoyl and Xaa_{28} is Asn or Ala.

[075] Preferred compounds of formula (V) include compounds described in WO 99/25727 and identified therein as Compound Nos. 62-69.

[076] Provided herein are exendin analogs wherein Xaai is His. Provided are those compounds of formula (V) wherein Xaa_2 is GIy. Provided are those compounds of formula (V) wherein Xaa3 is Ala. Provided are those compounds of formula (V) wherein $Xaai_4$ is Leu, pentylglycine or Met. Provided compounds of formula (V) are those wherein Xaa_{25} is Trp or Phe. Exemplary compounds of formula (V) are those where Xaa_6 is Ala, Phe or naphthylalanine; Xaa_{22} is Phe or naphthylalanine; and Xaa_{23} is He or VaI. Provided are compounds of formula (V) wherein Xaa3i, Xaa36, Xaa37 and Xaa38 are independently selected from Pro, homoproline, thioproline and N-alkylalanine. Preferably Zi is $-NH_2$. Preferably Z_2 is $-NH_2$.

[077] According to one embodiment, provided are compounds of formula (V) wherein Xaai is His or Tyr, more preferably His; Xaa_2 is Ala or GIy; Xaa_6 is Phe or naphthylalanine; $Xaai_4$ is Ala, Leu, pentylglycine or Met; Xaa_{22} is Phe or naphthylalanine; Xaa_{23} is He or VaI; Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from Pro, homoproline, thioproline or N-alkylalanine; and Xaa_{39} is Ser or Tyr, more preferably Ser. More preferably Zi is $-NH_2$.

[078] According to one embodiment, provided compounds include those of formula (V) wherein: Xaai is His; Xaa_2 is GIy or Ala; Xaa_3 is Ala, Asp or GIu; Xaa_4 is GIy; Xaa_5 is Ala or Thr; Xaa_6 is Phe or naphthylalanine; Xaa7 is Thr or Ser; Xaas is Ala, Ser or Thr; Xaa_9 is Asp or GIu; Xaaio is Ala, Leu or pentylglycine; Xaan is Ala or Ser; $Xaai_2$ is Ala or Lys; Xaai3 is Ala or GIn; Xaa_{14} is Ala, Leu, Met or pentylglycine; $Xaai_5$ is Ala or GIu; $Xaai_6$ is Ala or GIu; Xaan is Ala or GIu; Xaaig is Ala or VaI; Xaa_2o is Ala or Arg; Xaa_2i is Ala or Leu; Xaa_{22} is Phe or naphthylalanine; Xaa_{23} is He, VaI or tert-butylglycine; Xaa_{24} is Ala, GIu or Asp; Xaa_25 is Ala, Trp or Phe; Xaa_26 is Ala or Leu; Xaa_27 is Ala or Lys; Xaa_2s is Ala or Asn; Zi is -OH, $-NH_2$, GIy-Z_2, GIy GIy-Z_2, GIy GIy Xaa_3i-Z_2, GIy GIy Xaa_{31} Ser-Z_2, GIy GIy Xaa_{31} Ser Ser-Z_2, GIy GIy Xaa_{31} Ser Ser GIy-Z_2, GIy GIy Xaa_{31} Ser Ser GIy AIa-Z_2, GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_{36}-Z_2, GIy GIy Xaa_{31} Ser Ser GIy Ala Xaa_{36} Xaa_{37}-Z_2, GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_36 Xaa_37 Xaa_3s-Z_2 or GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_36 Xaa_37 Xaa_{38} Xaa_39-Z_2; Xaa_3i, Xaa_{36}, Xaa_37 and Xaa_3s being independently Pro homoproline, thioproline or N-methylalanine; and Z_2 being -OH or $-NH_2$; provided that no more than three of Xaa_3, Xaas, Xaa_6, Xaas, Xaaio, Xaan, $Xaai_2$, $Xaai_3$, $Xaai_4$, Xaais, Xaai6, Xaan, Xaaig, Xaa_{20}, Xaa_2i, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala; and provided also that, if Xaai is His, Arg or Tyr, then at least one of Xaa_3 and Xaa_4 is Ala.

[079] According to one embodiment, provided are compounds of formula (V) where $Xaai_4$ is Ala, Leu, He, VaI or pentylglycine, more preferably Leu or pentylglycine, and Xaa_25 is Ala, Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will be less susceptible to oxidative degradation, both in vitro and in vivo, as well as during synthesis of the compound.

[080] Particular compounds of formula (V) include those described in WO 99/25727 and having the amino acid sequences identified therein as SEQ ID NOS: 5-65 and 67-74, herein SEQ ID NOs: 23-91.

[081] Also provided for use in the formulation and methods described herein are peptides described in US Patent No. 7,220,72 1, including compounds of formula (VI) (SEQ ID NO:20) or a pharmaceutically acceptable salt thereof: Xaai Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa7 Xaas Xaag Xaaio Xaan $Xaai_2$ $Xaai_3$ $Xaai_4$ Xaais Xaai6 Xaan Ala Xaaig Xaa_2o Xaa_2i Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Zi; wherein Xaai is His, Arg, Tyr, Ala, Norval, VaI, Norleu or 4-imidazopropionyl; Xaa_2 is Ser, GIy, Ala or Thr; Xaa_3 is Ala, Asp or GIu; Xaa_4 is Ala, Norval, VaI, Norleu or GIy; Xaa_5 is Ala or Thr; Xaa_6 is Ala, Phe, Tyr or naphthylalanine; Xaa7 is Thr or Ser; Xaas is Ala, Ser or Thr; Xaag is Ala, Norval, VaI, Norleu, Asp or GIu; Xaaio is Ala, Leu, He, VaI, pentylglycine or Met; Xaan is Ala or Ser;

Xaa$_{12}$ is Ala or Lys; Xaai3 is Ala or GIn; Xaai$_{4}$ is Ala, Leu, He, pentylglycine, VaI or Met; Xaais is Ala or GIu; Xaai$_{6}$ is Ala or GIu; Xaa$_{17}$ is Ala or GIu; Xaai$_{9}$ is Ala or VaI; Xaa$_{2}$o is Ala or Arg; Xaa$_{2}$i is Ala, Leu or Lys-NH$^{\varepsilon}$-R where R is Lys, Arg, C$_{1-10}$ straight chain or branched alkanoyl or cycloalkyl-alkanoyl; Xaa$_{22}$ is Phe, Tyr or naphthylalanine; Xaa$_{23}$ is He, VaI, Leu, pentylglycine, tert-butylglycine or Met; Xaa$_{24}$ is Ala, GIu or Asp; Xaa$_{25}$ is Ala, Trp, Phe, Tyr or naphthylalanine; Xaa$_{2}$6 is Ala or Leu; Xaa$_{2}$7 is Lys, Asn, Lys-NH$^{\varepsilon}$-R or Ala where R is Lys, Arg, Ci-Ci$_{0}$ straight chain or branched alkanoyl or cyclo-alkylalkanoyl; Xaa$_{28}$ is Lys, Asn, Lys-NH$^{\varepsilon}$-R or Ala where R is Lys, Arg, Ci-Ci$_{0}$ straight chain or branched alkanoyl or cycloalkylalkanoyl; Z_1 is -OH, -NH$_{2}$, GIy-Z$_{2}$, GIy GIy-Z$_{2}$, GIy GIy Xaa$_{3}$i-Z$_{2}$, GIy GIy Xaa$_{3}$i Ser-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy AIa-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy Ala Xaa$_{36}$-Z$_{2}$, GIy GIy Xaa$_{31}$ Ser Ser GIy Ala Xaa$_{36}$ Xaa$_{37}$-Z$_{2}$, GIy GIy Xaa$_{3}$i Ser Ser GIy Ala Xaa$_{36}$ Xaa$_{37}$ Xaa$_{38}$-Z$_{2}$ or GIy GIy Xaa$_{3}$i Ser Ser GIy Ala Xaa$_{36}$ Xaa$_{37}$ Xaa$_{38}$ Xaa$_{39}$-Z$_{2}$; Xaa$_{3}$i, Xaa$_{36}$, Xaa$_{37}$ and Xaa$_{38}$ are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine and N-alkylalanine; Xaa$_{39}$ is Ser or Tyr; and Z$_{2}$ is -OH or -NH$_{2}$; provided that no more than three of Xaa$_{3}$, Xaa$_{4}$, Xaa$_{5}$, Xaa$_{6}$, Xaa$_{8}$, Xaag, Xaai$_{0}$, Xaan, Xaai$_{2}$, Xaai$_{3}$, Xaai$_{4}$, Xaais, Xaai$_{6}$, Xaa$_{17}$, Xaaig, Xaa$_{20}$, Xaa$_{2}$i, Xaa$_{24}$, Xaa$_{25}$, Xaa$_{26}$, are Ala; and provided also that, if Xaai is His, Arg, Tyr, or 4-imidazopropionyl then at least one of Xaa$_{3}$, Xaa$_{4}$ and Xaag is Ala.

[082] Exemplary compounds of formula (VI) include those wherein Xaai is His, Ala, Norval or 4-imidazopropionyl. Preferably, Xaai is His, or 4-imidazopropionyl or Ala, more preferably His or 4-imidazopropionyl. Exemplary compounds of formula (VI) include those wherein Xaa$_{2}$ is GIy. Exemplary compounds of formula (VI) include those wherein Xaa$_{4}$ is Ala. Exemplary compounds of formula (VI) include those wherein Xaag is Ala. Exemplary compounds of formula (VI) include those wherein Xaa$_{14}$ is Leu, pentylglycine or Met. Exemplary compounds of formula (VI) include those wherein Xaa$_{25}$ is Trp or Phe. Exemplary compounds of formula (VI) include those wherein Xaa6 is Ala, Phe or naphthylalanine; Xaa$_{22}$ is Phe or naphthylalanine; and Xaa$_{23}$ is He or VaI. Exemplary compounds of formula (VI) include those wherein Zi is -NH$_{2}$. Exemplary compounds of formula (VI) include those wherein Xaa$_{3}$i, Xaa$_{36}$, Xaa$_{37}$ and Xaa$_{38}$ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine. Exemplary compounds of formula (VI) include those wherein Xaa$_{39}$ is Ser. Exemplary compounds of formula (VI) include those wherein Z$_{2}$ is -NH$_{2}$. Exemplary compounds of formula (VI)

include those wherein Zi is $-NH_2$. Exemplary compounds of formula (VI) include those wherein Xaa_2i is Lys-NH^{ε}-R where R is Lys, Arg, C_1-C_{10} straight chain or branched alkanoyl. Exemplary compounds of formula (VI) include those wherein X_{27} is Lys or Lys-NH^{ε}-R, where R is Lys, Arg, Ci-Ci $_0$ straight chain or branched alkanoyl and $X_2$8 is Asn or Ala.

[083] Other compounds of formula (VI) include those described in WO 99/25728 as having an amino acid sequence selected from those identified therein as SEQ ID NOS: 95-110, and herein identified as SEQ ID NOS: 92-107.

[084] Compounds useful according to the formulations and methods described herein are exendin analog agonists described in U.S. Patent No. 6,956,026, including compounds of formula (VII) (SEQ ID NO:2 1) or a pharmaceutically acceptable salt thereof: Xaai Xaa_2 Xaa3 GIy Thr Xaa_6 Xaa7 Xaa_8 Xaag Xaai $_0$ Ser Lys GIn Xaai $_4$ GIu GIu GIu Ala VaI Arg Leu Xaa_{22} $Xaa_2$3 Xaa_{24} $Xaa_2$5 Leu Lys Asn GIy GIy Xaa_3i Ser Ser GIy Ala Xaa_{36} Xaa_{37} Xaa_{38} Xaa_{39}-Z; wherein: Xaai is His, Arg or Tyr; Xaa_2 is Ser, GIy, Ala or Thr; Xaa_3 is Asp or GIu; Xaa_6 is Phe, Tyr or naphthylalanine; Xaa_7 is Thr or Ser; Xaa_8 is Ser or Thr; Xaa_9 is Asp or GIu; Xaai $_0$ is Leu, He, VaI, pentylglycine or Met; Xaai $_4$ is Leu, He, pentylglycine, VaI or Met; Xaa_{22} is Phe, Tyr or naphthylalanine; Xaa_{23} is He, VaI, Leu, pentylglycine, tert-butylglycine or Met; Xaa_{24} is GIu or Asp; Xaa_{25} is Trp, Phe, Tyr, or naphthylalanine; Xaa_3i, $Xaa_3$6, $Xaa_3$7 and Xaa_{38} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkyl-alanine; Xaa_{39} is Ser, Thr or Tyr; and Z is -OH or $-NH_2$; with the proviso that the compound does not have the formula of either SEQ ID NOS: 1 or 2.

[085] Preferred N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups preferably of 1 to about 6 carbon atoms, more preferably of 1 to 4 carbon atoms. Exemplary exendin analogs include those wherein Xaai is His or Tyr. More preferably Xaai is His. Provided are those compounds wherein Xaa_2 is GIy. Provided are those compounds wherein Xaa_{14} is Leu, pentylglycine or Met. Exemplary compounds include those wherein $Xaa_2$5 is Trp or Phe. Also provided are compounds where Xaa_6 is Phe or naphthylalanine; Xaa_{23} is He or VaI and Xaa_3i, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from Pro, homoproline, thioproline or N-alkylalanine. Preferably N-alkylalanine has a N-alkyl group of 1 to about 6 carbon atoms. According to one embodiment, Xaa_{36}, Xaa_{37} and Xaa_{38} are the same amino acid reside. Provided are compounds wherein Xaa_{39} is Ser or Tyr, more preferably Ser. Preferably Z is $-NH_2$.

[086] According to one embodiment, provided are compounds of formula (VII)

wherein Xaai is His or Tyr, preferably His; Xaa_2 is GIy; Xaa_6 is Phe or naphthylalanine; Xaa_{14} is Leu, pentylglycine or Met; Xaa_{22} is Phe or naphthylalanine; $Xaa_2$3 is He or VaI; Xaa3i, Xaa36, Xaa37 and Xaa38 are independently selected from Pro, homoproline, thioproline or N-alkylalanine; and Xaa_{39} is Ser or Tyr, more preferably Ser. More preferably Z is $-NH_2$.

[087] According to another embodiment, exemplary compounds include those of formula (VII) wherein: Xaai is His or Arg; Xaa_2 is GIy; Xaa_3 is Asp or GIu; Xaa_6 is Phe or napthylalanine; Xaa_7 is Thr or Ser; Xaa_8 is Ser or Thr; Xaa_9 is Asp or GIu; Xaaio is Leu or pentylglycine; $Xaai_4$ is Leu or pentylglycine; Xaa_{22} is Phe or naphthylalanine; $Xaa_2$3 is He, VaI or t-butylglycine; Xaa_{24} is GIu or Asp; Xaa_{25} is Trp or Phe; Xaa_3i, Xaa_{36}, Xaa_{37}, and Xaa38 are independently Pro, homoproline, thioproline, or N-methylalanine; Xaa39 is Ser or Tyr: and Z is -OH or $-NH_2$; with the proviso that the compound does not have the formula of either SEQ ID NOS: 1 or 2. More preferably Z is $-NH_2$.

[088] According to another embodiment, provided are compounds where $Xaai_4$ is Leu, He, VaI or pentylglycine, more preferably Leu or pentylglycine, and Xaa_{25} is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds are believed to exhibit advantageous duration of action and to be less patient to oxidative degradation, both in vitro and in vivo, as well as during synthesis of the compound.

[089] Also provided for use in the formulations and methods described herein are compounds described in US Patent No. 7,157,555, including compounds of formula (VIII) (SEQ ID NO:22) or a pharmaceutically acceptable salt thereof:Xaai Xaa_2 Xaa_3 GIy Thr Xaa_6 Xaa_7 Xaas Xaag Xaaio Ser Lys GIn $Xaai_4$ GIu GIu GIu Ala VaI Arg Leu Xaa_{22} $Xaa_2$3 Xaa_{24} $Xaa_2$5 Leu $Xaa_2$7 Xaa_2s GIy GIy Xaa3i Ser Ser GIy Ala Xaa36 Xaa37 Xaa3s Xaa39-Z; wherein: Xaai is His, Arg, Tyr or 4-imidazopropionyl; Xaa_2 is Ser, GIy, Ala or Thr; Xaa_3 is Asp or GIu; Xaa_6 is Phe, Tyr or naphthylalanine; Xaa7 is Thr or Ser; Xaas is Ser or Thr; Xaa§ is Asp or GIu; Xaaio is Leu, He, VaI, pentylglycine or Met; Xaa_{14} is Leu, He, pentylglycine, VaI or Met; Xaa_{22} is Phe, Tyr or naphthylalanine; $Xaa_2$3 is He, VaI, Leu, pentylglycine, tert-butylglycine or Met; Xaa_{24} is GIu or Asp; Xaa_{25} is Trp, Phe, Tyr, or naphthylalanine; Xaa_{27} is Lys, Asn, or Lys-NH^{ε}-R where R is Lys, Arg, C_1-C_{10} straight chain or branched alkanoyl or cycloalkylalkanoyl; Xaa_2s is Lys, Asn, or Lys-NH^{ε}-R where R is Lys, Arg, Ci-Ci_0 straight chain or branched alkanoyl or cycloalkylalkanoyl; Xaa3i, Xaa36, Xaa37 and Xaa38 are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa39 is Ser, Thr or Tyr; and Z is -OH or $-NH_2$; with the proviso that the compound does not have the formula of either SEQ ID NOS: 1 or 2.

[090] Exemplary exendin analogs of formula (VIII) include those wherein Xaai is His, Tyr or 4-imidazopropionyl. More preferably, Xaai is His or 4-imidazopropionyl. Provided are those compounds of formula (VIII) wherein Xaa_2 is GIy. Provided are those compounds of formula (VIII) wherein Xaa_{14} is Leu, pentylglycine or Met. Provided are those compounds of formula (VIII) wherein Xaa_25 is Trp or Phe. Provided are those compounds of formula (VIII) wherein Xaa_27 is Lys or Lys-NH $^{\varepsilon}$-R where R is Lys, Arg, C_1-C_{10} straight chain or branched alkanoyl and Xaa_{28} is Asn.

[09 1] Also provided are compounds of formula (VIII) wherein Xaa_6 is Phe or naphthylalanine; Xaa_{22} is Phe or naphthylalanine; Xaa_23 is He or VaI and Xaa3i, Xaa36, Xaa37 and Xaa_{38} are independently selected from Pro, homoproline, thioproline or N-alkylalanine. According to one embodiment, Xaa39 is Ser or Tyr. Provide are compounds wherein Xaa39 is Ser. Preferably, Z is -NH_2.

[092] According to one embodiment, provided are compounds of formula (VIII) wherein Xaa_6 is Phe or naphthylalanine; Xaa_{22} is Phe or naphthylalanine; Xaa_23 is He or VaI; Xaa_27 is Lys or Lys-NH $^{\varepsilon}$-R where R is Lys, Arg, Ci-Ci $_0$ straight chain or branched alkanoyl, and Xaa_{28} is Asn; and Xaa3i, Xaa36, Xaa37 and Xaa38 are independently selected from Pro, homoproline, thioproline or N-alkylalanine.

[093] In another embodiment, exendins and exendin analogs of the invention do not include the peptides of SEQ ID NOS:3-14. In one embodiment, exendin analogs include the analogs of Formulas (I-VIII), with the proviso that the analogs do not include the peptides of SEQ ID NOs: 1-2.

[094] Also useful within the scope of the invention are narrower genera of compounds of the described formulae, for example formulae I through VIII, having peptides of various lengths, for example genera of compounds that do not include peptides having a length of greater than 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37 or 38 amino acid residues.

[095] The exendins, exendin agonists, or exendin analog agonists described herein may be in the form of a peptide, a pro-drug, or as a pharmaceutical salt or salts thereof. The term "prodrug" refers to a compound that is a drug precursor that, following administration, releases the drug *in vivo* via some chemical or physiological process, for example, proteolytic cleavage, or upon reaching an environment of a certain pH.

[096] Exendins, exendin analog agonists and exendin agonists that are peptides, described herein may be prepared through peptide purification as described in, for example, Eng et al, *J. Biol Chem.*, 265:20259-62 (1990); and Eng et al, *J. Biol Chem.*, 267:7402-05

(1992), which are incorporated by reference herein. Alternatively, exendins, exendin peptide agonists and exendin analog agonists may be prepared by methods known to those skilled in the art, for example, as described in Raufman et al, *J. Biol. Chem.*, 267:21432-37 (1992), which is incorporated by reference herein, using standard solid-phase peptide synthesis techniques, for example, using an automated or semiautomated peptide synthesizer. Typically, using such techniques, an α-N-carbamoyl protected amino acid and an amino acid attached to the growing peptide chain on a resin are coupled at room temperature in an inert solvent such as dimethylformamide, N-methylpyrrolidinone or methylene chloride in the presence of coupling agents such as dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in the presence of a base such as diisopropylethylamine. The α-N-carbamoyl protecting group is removed from the resulting peptide-resin using a reagent such as trifluoroacetic acid or piperidine, and the coupling reaction repeated with the next desired N-protected amino acid to be added to the peptide chain. Suitable N-protecting groups are well known in the art, with, for example, t-butyloxycarbonyl (tBoc) and fluorenylmethoxycarbonyl (Fmoc).

[097] The solvents, amino acid derivatives and 4-methylbenzhydryl-amine resin used in the peptide synthesizer may be purchased from Applied Biosystems Inc. (Foster City, CA). The following side-chain protected amino acids may be purchased from Applied Biosystems, Inc.: BSD-1 12344. l-Arg(Pmc), Boc-Thr(Bzl), Fmoc-Thr(t-Bu), Boc-Ser(Bzl), Fmoc-Ser(t-Bu), Boc-Tyr(BrZ), Fmoc-Tyr(t-Bu), Boc-Lys(Cl-Z), Fmoc-Lys(Boc), Boc-GIu(BzI), Fmoc-Glu(t-Bu), Fmoc-His(Trt), Fmoc-Asn(Trt), and Fmoc-Gln(Trt). Boc-His(BOM) may be purchased from Applied Biosystems, Inc. or Bachem Inc. (Torrance, CA). Anisole, dimethylsulfide, phenol, ethanedithiol, and thioanisole may be obtained from Aldrich Chemical Company (Milwaukee, WI). Air Products and Chemicals (Allentown, PA) supplies HF. Ethyl ether, acetic acid and methanol may be purchased from Fisher Scientific (Pittsburgh, PA).

[098] Solid phase peptide synthesis may be carried out with an automatic peptide synthesizer (Model 430A, Applied Biosystems Inc., Foster City, CA) using the NMP/HOBt (Option 1) system and tBoc or Fmoc chemistry (see, Applied Biosystems User's Manual for the ABI 430A Peptide Synthesizer, Version 1.3B July 1, 1988, section 6, pp. 49-70, Applied Biosystems, Inc., Foster City, CA) with capping. Boc-peptide-resins may be cleaved with HF (-50^{0}C to 0^{0}C, 1 hour). The peptide may be extracted from the resin with alternating water and acetic acid, and the filtrates lyophilized. The Fmoc-peptide resins may be cleaved according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems,

Inc., 1990, pp. 6-12). Peptides may also be assembled using an Advanced Chem Tech Synthesizer (Model MPS 350, Louisville, Kentucky).

[099] Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters Delta Prep 3000 system. A C4, C8 or C18 preparative column (10 μ, 2.2 x 25 cm; Vydac, Hesperia, CA) may be used to isolate peptides, and purity may be determined using a C4, C8 or C18 analytical column (5 μ, 0.46 x 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH_3CN) may be delivered to the analytical column at a flowrate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed on the Waters Pico Tag system and processed using the Maxima program. Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115°C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen, et al., The Pico Tag Method: A Manual of Advanced Techniques for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, MA (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, PA). Mass calibration may be performed using cesium iodide or cesium iodide/glycerol. Plasma desorption ionization analysis using time of flight detection may be carried out on an Applied Biosystems Bio-Ion 20 mass spectrometer. Electrospray mass spectroscopy may be carried and on a VG-Trio machine.

[0100] Exendins, exendin analog agonists and exendin agonists that are peptides may also be prepared using recombinant DNA techniques, using methods now known in the art. See, e.g., Sambrook et al, Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor (1989). Alternatively, such compounds may be prepared by homogeneous phase peptide synthesis methods. Non-peptide compounds useful in the invention may be prepared by art-known methods. For example, phosphate-containing amino acids and peptides containing such amino acids, may be prepared using methods known in the art. See, e.g., Bartlett and Landen, *Biorg. Chem.*, 14:356-377 (1986).

[0101] Exendins, exendin agonists or exendin analog agonists may be formulated into pharmaceutical compositions for administration to patients. These pharmaceutical compositions preferably include an amount of an exendin, an exendin agonist or exendin analog agonist effective to lower total cholesterol, lower LDL cholesterol, lower triglyceride levels, or treat dyslipidemia or atherosclerosis, and a pharmaceutically acceptable carrier.

[0102] In any of the embodiments described herein, the patient may be a mammal, including a human or an animal. The animal may be a domestic animal, such as a companion animal (e.g., dog, cat, horse) or livestock (e.g., sheep, cow, pig, buffalo, ostrich, chicken, turkey).

[0103] The compositions described herein may be administered parenterally, orally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In one embodiment, the compositions are administered by an infusion pump or subcutaneous injection of a slow release, extended release, sustained release or long acting formulation. In one embodiment, subcutaneous injections are administered once a day; once every two, three, four, five, or six days; once per week; twice per month; once a month; every other month or every third month.

[0104] Any of the exendins, exendin agonists or exendin analog agonists may be administered in the acid or amide form. Additionally, any of the exendins, exendin agonists or exendin analog agonists may form salts with various inorganic and organic acids and bases. Such salts include, without limitation, salts prepared with organic and inorganic acids, for example, HCl, HBr, H_2SO_4, H_3PO_4, trifluoroacetic acid, acetic acid, formic acid, methanesulfonic acid, toluenesulfonic acid, maleic acid, fumaric acid and camphorsulfonic acid. Salts prepared with bases include, without limitation, ammonium salts, alkali metal salts, e.g., sodium and potassium salts, and alkali earth salts, e.g., calcium and magnesium salts. Acetate, hydrochloride, and trifluoroacetate salts are particular examples. The salts may be formed by conventional means, as by reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

[0105] Pharmaceutically acceptable carriers useful in these pharmaceutical compositions include, e.g., ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0106] Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art, using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms, including emulsions and suspensions. Other commonly used surfactants, such as TWEENs, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0107] Parenteral formulations may be a single bolus dose, an infusion, or a loading bolus dose followed with a maintenance dose. These compositions may be administered according to any dosage schedule described herein.

[0108] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0109] The pharmaceutical compositions of this invention may also be administered topically. For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water.

[0110] The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[011 1] The amount of exendin, exendin agonist or exendin analog agonist that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. The compositions can be formulated so that a dosage of between 0.1-1000 pmoles/kg body weight/minute (when administered by infusion) of exendin, exendin agonists or exendin analog agonist is administered to a patient receiving these compositions. In some embodiments of the invention, the dosage is 1-10 pmoles/kg body weight/minute (when administered by infusion). In one embodiment the dosage is 0.5-2.0 pmoles/kg/min when administered by intravenous infusion.

[0112] The pharmaceutical formulations comprising the exendin, exendin agonist or exendin analog agonist may be administered as a single dose or multiple doses. In embodiment, the pharmaceutical formulation dosage is about 0.8 mg containing about 5% of an exendin, exendin agonist, or exendin analog agonist, such as, for example, exendin-4. In another embodiment, the pharmaceutical formulation dosage is about 2.0 mg containing about 5% of an exendin, exendin agonist, or exendin analog agonist, such as, for example, exendin-4. In additional embodiments, the pharmaceutical formulation dosage is about 0.5 mg, about 0.8 mg, about 1.0 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2.0 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3.0 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4.0 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5.0 mg, or any range between a lower amount and a higher amount within these described dosages (e.g., about 0.5 mg to about 5.0 mg; about 1.75 mg to about 2.25 mg, and the like) where the pharmaceutical formulation dosage contains from about 1% to about 20%, from about 2% to about 10%, about 3% to about 7%; or about 5% of an exendin, exendin agonist, or exendin analog agonist, such as, for example, exendin-4. The skilled artisan can make any necessary dosage adjustments in order to obtain the effective plasma concentrations of an exendin, exendin agonist or exendin analog agonist suitable for use in the methods described herein.

[0113] In other embodiments, the pharmaceutical formulations described herein may contain from about from about 20 μg to about 400 μg; from about 30 μg to about 300 μg; or from about 50 μg to about 200 μg of an exendin, exendin agonist, or exendin analog agonist. In one embodiment, the pharmaceutical formulation is in a form that can be administered subcutaneously. In another embodiment, the pharmaceutical formulation is a polymer-based formulation that can be administered subcutaneously. The skilled artisan can make any necessary adjustments to the amount of the exendin, exendin agonist, or exendin analog agonist used in the pharmaceutical formulations in order to obtain the effective plasma concentrations of the exendin, exendin agonist or exendin analog agonist suitable for use in the methods described herein.

[0114] In another embodiment, the exendins exendin agonists or exendin analog agonists are formulated in a sustained release or long acting formulation. In one embodiment, the sustained release formulation comprises a biocompatible polymer, an exendin, or exendin analog agonist, and a sugar. Exemplary formulations are described in U.S. Patent No. 6,824,822; US Publication No. 2006/0099271; US Publication No. 2004/0228833; US Publication No. 2004/0208929; US Publication No. 2005/0271702; and US Publication No. 2006/01 10423, the disclosures of which are incorporated by reference herein in their entirety. Such formulations can be administered, for example by subcutaneous injection, once per day, every 2 days, 3 days, 4 days, 5 days, or 6 days; once per week, once every 2 weeks, or once every three weeks; or once per month, once every other month or once every 3 months.

[0115] Sustained release compositions can be prepared by a phase separation process. The general process for producing a sustained release or long acting formulation comprising microparticles containing an exendin, exendin agonist or exendin analog agonist and sucrose for a 1 kg batch size is described below.

[0116] A water-in-oil emulsion is created with the aid of a homogenizer. Suitable homogenizers include an in-line Megatron homogenizer MT-V 3-65 F/FF/FF, Kinematica AG, Switzerland. The water phase of the emulsion can be prepared by dissolving an exendin, exendin agonist or exendin analog agonist, for example, exendin-4, and excipients such as sucrose in water. The concentration of exendin in the resulting solution can be from about 50 mg/g to about 100 mg/g. For example, when the drug is exendin-4, the concentration of drug in solution can be from about 30 g to about 60 g per 600 g of water. In a particular embodiment, 50 g exendin-4 and 20 g sucrose are dissolved in 600 g water for irrigation (WFI). The specified amounts listed above represent a nominal load without adjustment to compensate for peptide content strength specific to the lot of exendin-4 used. The oil phase of the emulsion is prepared by dissolving PLGA polymer *(e.g.,* 930 g of purified 50:50 DL4A PLGA (Alkermes, Inc.) in methylene chloride (14.6 kg or 6% w/w)).

[0117] The water phase is then added to the oil phase to form a coarse emulsion with an overhead mixer for about three minutes. Then, the coarse emulsion is homogenized at approximately 21300 rpm at ambient temperature for three discrete periods. This should result in an inner emulsion droplet size of less than 1 micron. It is understood that inner emulsion formation can be achieved using any suitable means. Suitable means of emulsion formation include, but are not limited to, homogenization as described above and sonication.

[0118] A coacervation step is then performed by adding silicone oil (21.8 kg of Dimethicone, NF, 350 cs) over a time period of less than or equal to about 5 minutes to the inner emulsion. This is equivalent to a ratio of 1.5:1, silicone oil to methylene chloride. The methylene chloride from the polymer solution partitions into the silicone oil and begins to precipitate the polymer around the water phase containing the exendin, leading to microencapsulation. The embryonic microspheres thus formed are soft and require hardening. Frequently, the embryonic microspheres are permitted to stand for a short period of time, for example, less than 1 minute or from about 1 minute to about 5 minutes prior to proceeding to the microsphere hardening step.

[0119] The embryonic microspheres are immediately transferred into a heptane/ethanol solvent mixture. The volume of heptane/ethanol mixture needed can be determined based on the microsphere batch size, typically a 16:1 ratio of heptane/ethanol solvent to methylene chloride. For example, about 210 kg heptane and 23 kg ethanol in a 3^0C cooled, stirred tank can be used. This solvent mixture hardens the microspheres by extracting additional methylene chloride from the microspheres. This hardening step can also be referred to as quenching. After being quenched for 1 hour at 3°C, the solvent mixture is either decanted and fresh heptane (13 Kg) is added at 3^0C and held for 1 hour to rinse off residual silicone oil, ethanol and methylene chloride on the microsphere surface or pumped directly to the collection step.

[0120] At the end of the quench or decant/wash step, the microspheres are transferred and collected, for example, on a 12" Sweco Pharmasep Filter/Dryer Model PH12Y6. In this example, the filter/dryer uses a 25 micron multilayered collection screen and is connected to a motor that vibrates the screen during collection and drying. A final rinse with heptane (6 Kg at 3°C) can be performed to ensure maximum line transfer and to remove any excess silicone oil. The microspheres can then be dried under vacuum with or without a constant purge of nitrogen gas at controlled rate, for example,: 3 to 10 hours (e.g. 6 hours) at 3°C; 3 to 10 hours ramping to 41°C (e.g. 6 hours); and maintaining for a long period (e.g. 80-90 hours) at 41°C. After the completion of drying, the microspheres are discharged into a collection vessel, sieved through a 150 μm sieve, and stored at about -20 °C until filling.

[0121] An alternative general process for producing a sustained release or long acting formulation comprising microparticles containing an exendin, exendin agonist or exendin analog agonist and sucrose is as follows: A water-in-oil emulsion is created with the aid of a sonicator. Suitable sonicators include Vibracell VCX 750 with model CV33 probe head, Sonics and Materials Inc., Newtown, CT. The water phase of the emulsion is prepared by dissolving an exendin, for example, exendin-4, and excipients such as sucrose in water. The concentration of drug in the resulting solution can be from about 50 mg/ml to about 100 mg/ml. For example, when the drug is exendin-4, the concentration of drug in solution can be from about 3.28 g to about 6.55 g per 65.5 g of water. In a particular embodiment, 5.46 g exendin-4 and 2.18 g sucrose are dissolved in 65.5 g water for irrigation or WFI. The specified amounts listed above represent a 4% overage to target load in order to compensate for losses upon filter sterilization of the components. The oil phase of the emulsion is prepared by dissolving PLGA polymer *(e.g.,* 97.7 g of purified 50:50 DL4A PLGA (Alkermes, Inc.)) in methylene chloride (1539 g or 6% w/v).

[0122] The water phase is then added to the oil phase over about a three-minute period while sonicating at 100% amplitude at ambient temperature. The water phase containing the sucrose/exendin-4 is charged to the coacervation reactor. Reactor is then stirred at 1400 to 1600 rpm, with additional sonication at 100% amplitude for 2 minutes, followed by a 30 second hold, and then 1 minute more of sonication. This results in an inner emulsion droplet size of less than 0.5 microns. It is understood that inner emulsion formation can be achieved using any suitable means. Suitable means of emulsion formation include, but are not limited to, sonication as described above and homogenization.

[0123] A coacervation step is then performed by adding silicone oil (2294 gr of Dimethicone, NF, 350 cs) over time period of less than five minutes to the inner emulsion. This is equivalent to a ratio of 1.5:1, silicone oil to methylene chloride. The methylene chloride from the polymer solution partitions into the silicone oil and begins to precipitate the polymer around the water phase containing exendin, leading to microencapsulation. The embryonic microspheres thus formed are soft and require hardening. Frequently, the embryonic microspheres are permitted to stand for a short period of time, for example, of less than 1 minute or from about 1 minute to about 5 minutes prior to proceeding to the microsphere hardening step.

[0124] The embryonic microspheres are then immediately transferred into a heptane/ethanol solvent mixture. The volume of heptane/ethanol mixture needed can be determined based on the microsphere batch size. In the present example, about 22 kg heptane and 2448 g ethanol in a 3°C cooled, stirred tank (350 to 450 rpm) are used. This solvent mixture hardens the microspheres by extracting additional methylene chloride from the microspheres. This hardening step can also be referred to as quenching. After being quenched for 1 hour at 3^0C, the solvent mixture is decanted and fresh heptane (13 Kg) is added at 3°C and held for 1 hour to rinse off residual silicone oil, ethanol and methylene chloride on the microsphere surface.

[0125] At the end of the rinse step, the microspheres are transferred and collected, for example, on a 6" diameter, 20 micron multilayered screen inside the cone shaped drying chamber which acts as a dead-end filter. A final rinse with heptane (6 Kg at 4°C) is performed to ensure maximum line transfer. The microspheres are then dried with a constant purge of nitrogen gas at a controlled rate, for example, according to the following schedule: 18 hours at 3°C; 24 hours at 25°C; 6 hours at 35°C; and 42 hours at 38°C.

[0126] After the completion of drying, the microspheres are discharged into a teflon/stainless steel sterilized collection vessel attached to the drying cone. The collection vessel is sealed, removed from the drying cone and stored at -20 ± 5°C until filling. Material remaining in the cone upon disassembly for cleaning is taken for drug content analysis.

[0127] Non-limiting examples of specific PLG polymers suitable for use in the general methods described above are listed below. The listed polymers can be obtained from Lakeshore Biomaterials of Birmingham, Alabama, or Boehringer Ingelheim Pharma GmbH & Co. KG, Germany, although other sources may be available, and can be described as follows: Polymer 2A: Poly(lactide-co-glycolide); 50:50 lactide:glycolide ratio; 12.3 kD MoI. Wt.; rV=0.15 (dL/g). Polymer 4A: Poly(lactide-co-glycolide); 50:50 lactide:glycolide ratio; MoI. Wt. 45-64 kD; IV=0.45-0.47 (dL/g).

[0128] It is known in the art that proteins and peptides which are incorporated in PLG matrices can be undesirably altered (e.g., degraded or chemically modified) as a result of interaction with degradation products of the PLG or impurities remaining after preparation of the polymer. Lucke et al., *Pharmaceutical Research*, 19(2): 175-181 (2002). As such, the PLG polymers used in the preparation of microparticle formulations described herein can be purified prior to preparation of the sustained release compositions using art recognized purification methods.

EXAMPLES

[0129] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[0130] The pharmacokinetics of a long-acting release formulation of exenatide was evaluated in a study in patients with Type 2 diabetes. The study population consisted of individuals with type 2 diabetes treated with a stable regimen of oral diabetes medications or managed with diet modification and exercise. Patients, male or female, had a mean age of 55±10 years with a mean body mass index (BMI) of about 34.9 kg/m^2 at screening, and a mean $HbAi_c$ of 9.3±1.0% at screening. The 30 week study compared a 10 μg formulation of exenatide administered twice daily (BID) by subcutaneous (SC) injection and a 2 mg formulation of exenatide administered once weekly by subcutaneous (SC) injection. The study was also conducted, *inter alia,* to examine the effects of such administration on the individual's total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride levels, hemoglobin A_{1C}, fasting postprandial blood glucose, and weight.

[0131] During the 3-day lead-in period, patients self-administered exenatide 5 μg SC, BID, within 15 minutes prior to meals in the morning and evening. The exenatide 5 μg SC, BID used in the 3-day lead-in period was a clear, colorless, sterile preserved solution for SC injection containing exenatide (exendin-4) in sodium acetate buffer, pH 4.5, 4.3% mannitol as an iso-osmolality modifier and 0.22% metacresol as a preservative. The strength of exenatide injection was 0.25 mg/mL of exendin-4. This 3-day lead-in period was designed to expose patients to exenatide prior to administration of exenatide 10 μg BID or exenatide once weekly to determine if a patient may exhibit an acute sensitivity to exenatide.

[0132] During the 30-week treatment period, patients received once weekly subcutaneous injections of a 2.0 mg dose pharmaceutical formulation containing 5% exenatide or patient received twice daily subcutaneous injections of exenatide at 10 μg per dose.

[0133] Exenatide once weekly is a sustained-release formulation of exenatide (exendin-4) designed to provide exenatide release over a period ranging from 7 to 91 days. Exenatide once weekly used in this study contained, on a w/w basis, 5% exenatide, 2% sucrose, and 93% MEDISORB® 50:50 poly D,L-lactic co-glycolic acid (also referred to as "poly(lactide-co-glycolide)"). The vial containing the white to off-white dry powder (2.8 mg of exenatide once weekly) was stored frozen in a freezer with a recorded temperature at ≤ -20 ± 5^{0}C at the study site.

[0134] Patients were monitored about every four weeks for body weight, vital signs (including blood pressure, heart rate, respiratory rate, and temperature), urinalysis, and adverse events. In addition, blood was drawn to assess plasma concentrations of exendin-4 and blood lipids.

[0135] Plasma exenatide was quantified by a validated Enzyme-Linked Immunosorbent Assay (ELISA) at Millipore (Billerica, MA). Fineman et al, *Diabetes Care,* 26:2370-2377 (2003). Glycosylated hemoglobin was quantitated by Quintiles Laboratories (Smyrna, GA) using high-performance liquid chromatography. Davis et al, *Diabetes,* 27:102-107 (1978); Cole et al, *Metabolism,* 27:289-301 (1978).

[0136] **Figure 1** shows the plasma concentration of exendin-4 over a period of 30 weeks. The average plasma concentration at week 30 was about 388 pg/mL for a 2.0 mg dose of a pharmaceutical formulation containing 5% exendin-4. The geometric mean plasma concentration of exendin-4 at week 30 was about 300 pg/mL for a 2.0 mg dose of a pharmaceutical formulation containing 5% exendin-4. The range of the geometric mean plasma concentration of exendin-4 at week 30 was about 145 pg/mL to about 700 pg/mL for a 2.0 mg dose of a pharmaceutical formulation containing 5% exendin-4.

[0137] For exenatide once weekly, fasting triglycerides levels decreased by an average of 42 mg/dL from baseline to week 30 in a group of 148 patients, as shown in **Figure 2A.** For exenatide BID, fasting triglycerides levels decreased by an average of 22 mg/dL from baseline to week 30 in a group of 147 patients, as shown in **Figure 2B.**

[0138] For exenatide once weekly, the total cholesterol and LDL-cholesterol decreased by an average of 11.9 mg/dL and 4.9 mg/dL, respectively from baseline to week 30, as shown in **Figures 3A** and **3C.** For exenatide BID, the total cholesterol decreased by an average of 3.8 mg/dL from baseline to week 30, as shown in Figure 3B, and the LDL-cholesterol increased by an average of 1.2 mg/dL from baseline to week 30, as shown in Figure **3D.** As shown in **Figures 3E** and **3F,** HDL-cholesterol decreased by 0.9 mg/dL and

1.3 mg/dL from baseline to week 30 for exenatide once weekly and exenatide BID, respectively.

[0139] **Figure 4** shows the weight loss associated with exenatide once weekly and exenatide BID. For exenatide once weekly, **Figure 4A** shows that the weight loss from baseline to week 30 was about 3.7 kg. For exenatide BID, **Figure 4B** shows that the weight loss from baseline to week 30 was about 3.6 kg.

[0140] **Figure 5A** shows that HbAic decreased by an average of 1.9% from baseline to week 30 in patients receiving exenatide once weekly. **Figure 5B** shows that HbAic decreased by an average of 1.5% from baseline to week 30 in patients receiving exenatide BID.

[0141] **Figure 6A** shows that fasting postprandial blood glucose decreased by an average of 42 mg/dL from baseline to week 30 in patient receiving exenatide once weekly, while **Figure 6B** shows that fasting postprandial blood glucose decreased by an average of 25 mg/dL from baseline to week 30 in patient receiving exenatide BID.

[0142] All publications, patents, patent applications, and other references cited in this application are hereby incorporated by reference in their entirety as if each individual publication, patent, patent application, or other reference was specifically and individually indicated to be incorporated by reference.

[0143] The detailed description provided herein is to aid the skilled artisan in practicing the invention. This detailed description should not be construed to unduly limit the invention as modifications and variations in the embodiments discussed herein can be made by one of ordinary skill in the art without departing from the spirit or scope of the inventive discovery.

CLAIMS

What is claimed is:

1. A method for reducing total cholesterol levels, reducing LDL-cholesterol levels, or reducing triglyceride levels in a patient in need thereof comprising identifying a patient in need of a reduction in total cholesterol levels, LDL-cholesterol levels, or triglyceride levels; and administering to the patient a pharmaceutical formulation comprising at least one exendin, exendin agonist or exendin analog agonist in an amount sufficient to maintain a steady state average or minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist at a level of at least 100 pg/ml for at least one week to reduce the total cholesterol levels, LDL-cholesterol levels, or triglyceride levels in the patient.

2. A method for lowering total cholesterol levels, LDL-cholesterol levels, or triglyceride levels in a patient in need thereof comprising: identifying a patient in need of a reduction in total cholesterol levels, LDL-cholesterol levels, or triglyceride levels; and administering to the patient a pharmaceutical formulation comprising at least one exendin, exendin agonist or exendin analog agonist in an amount sufficient to maintain a steady state geometric mean plasma concentration of the exendin, exendin agonist or exendin analog agonist of about 145 pg/mL to about 700 pg/mL to reduce total cholesterol levels, LDL-cholesterol levels, or triglyceride levels in the patient.

3. A method for treating dyslipidemia or atherosclerosis in a patient in need thereof comprising identifying a patient in need of treatment for dyslipidemia or atherosclerosis; and administering to the patient a pharmaceutical formulation comprising at least one exendin, exendin agonist or exendin analog agonist in an amount sufficient to maintain a steady state average or minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist at a level of at least 100 pg/ml for at least one week to treat dyslipidemia or atherosclerosis in the patient.

4. The method of claim 1, 2, or 3, wherein the exendin, exendin agonist, or exendin analog agonist is exendin-4, an exendin-4 agonist, or an exendin-4 analog agonist.

5. The method of claim 1, 2, or 3, wherein the exendin, exendin agonist, or exendin analog agonist is exendin-4.

6. The method of claim 1, 2, or 3, wherein the exendin, exendin agonist, or exendin analog agonist is a peptide having at least 90% sequence identity to exendin-4.

7. The method of claim 1, 2, or 3, wherein the pharmaceutical formulation comprises the exendin, exendin agonist, or exendin analog agonist in an amount of about 20 μg to about 200 μg.

8. The method of claim 1, 2, or 3, wherein the dosage of the pharmaceutical formulation is from about 0.5 mg to about 5 mg, and wherein the dosage comprises from about 1% to about 20% of the exendin, exendin agonist, or exendin analog agonist.

9. The method of claim 1, 2, or 3, wherein the administration is peripheral administration.

10. The method of claim 1, 2, or 3, wherein the administration is subcutaneous.

11. The method of claim 1 or 3, comprising administering to the patient the pharmaceutical formulation comprising at least one exendin, exendin agonist or exendin analog agonist in an amount sufficient to maintain the steady state average plasma concentration of the exendin, exendin agonist, or exendin analog agonist.

12. The method of claim 1 or 3, wherein the average or minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist is at the steady state for about one week to about three months.

13. The method of claim 1 or 3, wherein the steady state average or minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist at a level of about 145 pg/mL to about 750 pg/mL.

14. The method of claim 1 or 3, wherein the steady state average or minimum plasma concentration of the exendin, exendin agonist, or exendin analog agonist at a level of about 200 pg/mL to about 600 pg/mL.

15. The method of claim 1, 2, or 3, wherein the pharmaceutical formulation further comprises at least one polymer.

16. The method of claim 15, wherein the polymer is poly(lactide-co-glycolide).

17. Use of an exendin, exendin agonist, or exendin analog agonist in the manufacture of a medicament that maintains a steady state average plasma concentration of the exendin, exendin agonist, or exendin analog agonist at a level of at least 100 pg/ml for at least one week for use in lowering total cholesterol levels; lowering LDL-cholesterol levels; lowering triglyceride levels; treating dyslipidemia; or treating atherosclerosis.

18. A method for treating diabetes in a patient in need thereof comprising identifying a patient in need of treatment for diabetes; and subcutaneously administering to the patient a pharmaceutical formulation comprising at least one polymer and a sufficient amount of exendin-4 to maintain a steady state geometric mean plasma concentration of exendin-4 at a level of about 145 pg/mL to about 700 pg/mL to treat diabetes in the patient.

19. The method of claim 18, wherein the diabetes is type I diabetes, type II diabetes, or gestational diabetes.

20. A method for reducing postprandial blood glucose or hemoglobin A_1C in a patient in need thereof comprising: identifying a patient in need of a reduction in postprandial blood glucose or hemoglobin A_1C; and subcutaneously administering to the patient a pharmaceutical formulation comprising at least one polymer and a sufficient amount of exendin-4 to maintain a steady state geometric mean plasma concentration of exendin-4 at a level of about 145 pg/mL to about 700 pg/mL to reduce postprandial blood glucose or hemoglobin A_1C in the patient.

21. A method for treating obesity in a patient in need thereof comprising: identifying a patient in need of treatment for obesity; and subcutaneously administering to the patient a pharmaceutical formulation comprising at least one polymer and a sufficient amount of exendin-4 to maintain a steady state geometric mean plasma concentration of exendin-4 at a level of about 145 pg/mL to about 700 pg/mL to treat obesity in the patient.

22. A method for lowering total cholesterol levels, LDL-cholesterol levels, or triglyceride levels in a patient in need thereof comprising: identifying a patient in need of a reduction in total cholesterol levels, LDL-cholesterol levels, or triglyceride levels; and subcutaneously administering to the patient a pharmaceutical formulation comprising at least one polymer and a sufficient amount of exendin-4 to maintain a steady state geometric mean plasma concentration of the exendin-4 at a level of about 145 pg/mL to about 700 pg/mL to reduce total cholesterol levels, LDL-cholesterol levels, or triglyceride levels in the patient.

23. The method of claim 18, 20, 21, or 22, wherein the geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist is about 200 pg/ml to about 400 pg/ml.

24. The method of claim 18, 20, 21, or 22, wherein the geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist is 175 pg/ml to 650 pg/ml.

25. The method of claim 18, 20, 21, or 22, wherein the geometric mean plasma concentration of the exendin, exendin agonist, or exendin analog agonist is 200 pg/ml to 600 pg/ml.

26. The method of claim 18, 20, 21, or 22, wherein the amount of exendin-4 in the pharmaceutical formulation is from about 20 μg to about 200 μg.

27. The method of claim 18, 20, 21, or 22, wherein the dosage of the pharmaceutical formulation is from about 0.5 mg to about 4 mg, and wherein the dosage comprises from about 2% to about 10% of the exendin-4.

28. The method of claim 18, 20, 21, or 22, wherein the polymer is poly(lactide-co-glycolide).

29. The method of claim 28, wherein the ratio of lactide:glycolide is from 20:80 to 80:20.

30. The method of claim 28, wherein the ratio of lactide:glycolide is 50:50.

31. The method of claim 18, 20, 21, or 22, wherein the pharmaceutical formulation comprises one, two or three polymers.

32. The method of claim 1, 2, 3, 17, 18, 20, 21, or 22, wherein the pharmaceutical formulation comprises about 5% (w/w) of exenatide, about 2% (w/w) of sucrose, and about 93% (w/w) of a poly(lactide-co-glycolide) polymer.

Figure 1

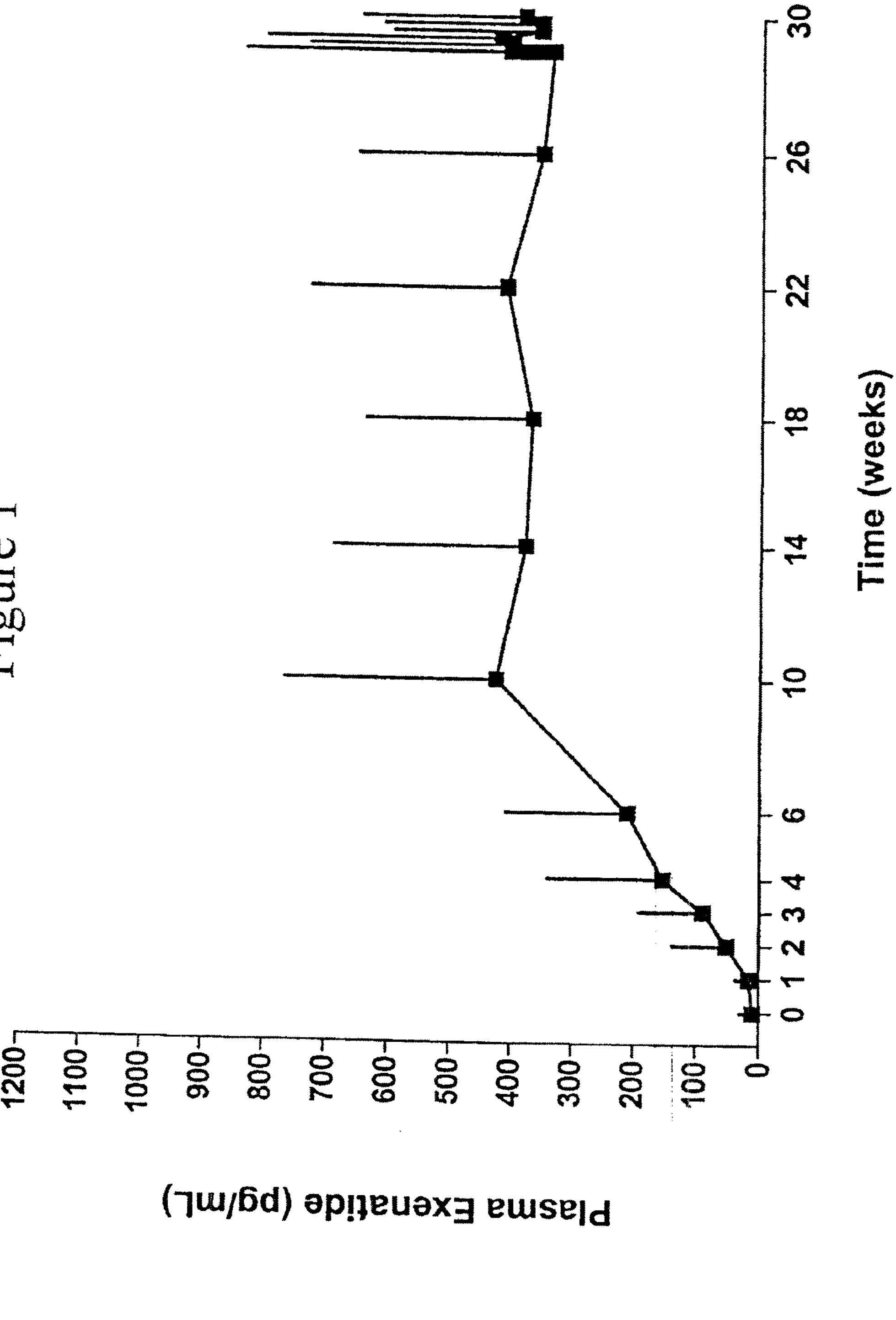

Plasma Exenatide (pg/mL)
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
Time (weeks)
0 1 2 3 4 6 10 14 18 22 26 30

Figure 2

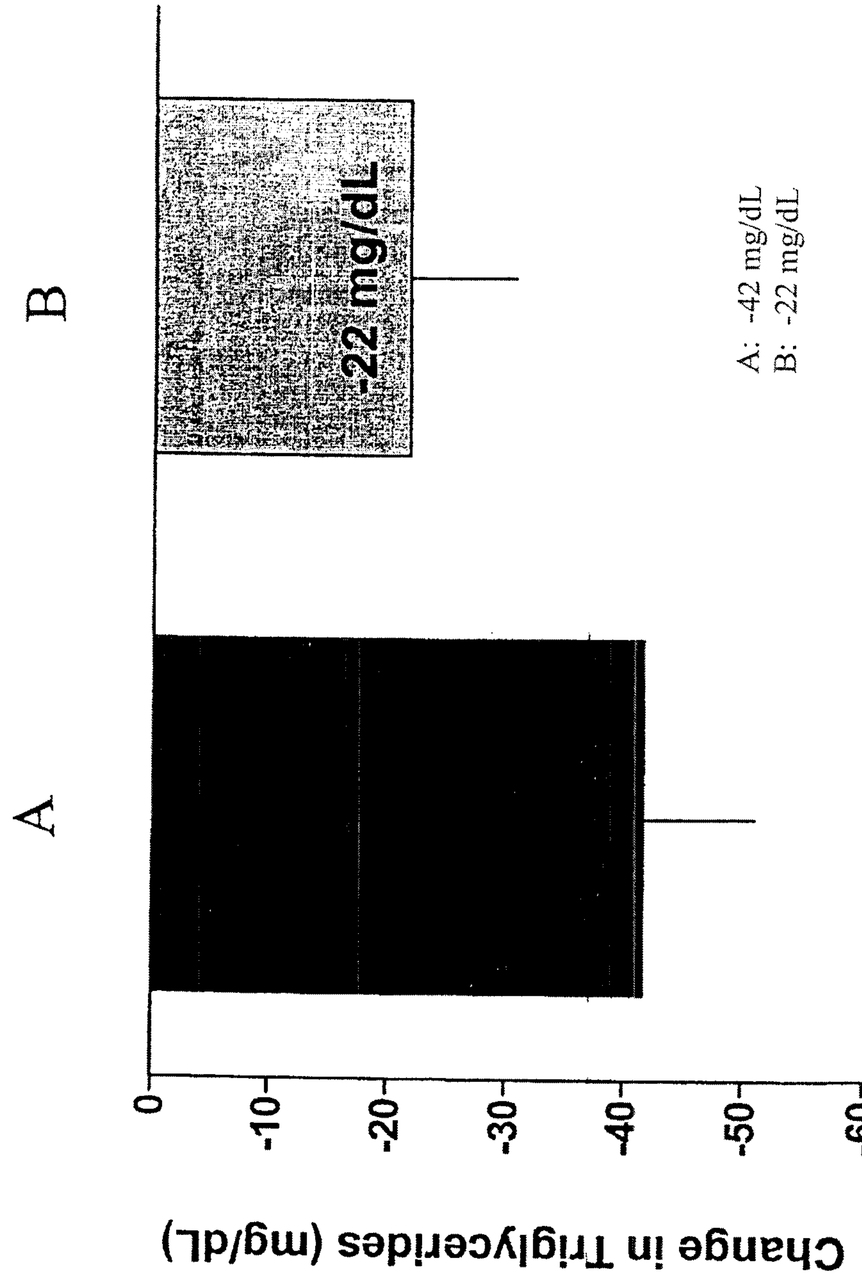

A
B
-22 mg/dL
0
-10
-20
-30
-40
-50
-60
Change in Triglycerides (mg/dL)
A: -42 mg/dL
B: -22 mg/dL

Figure 3

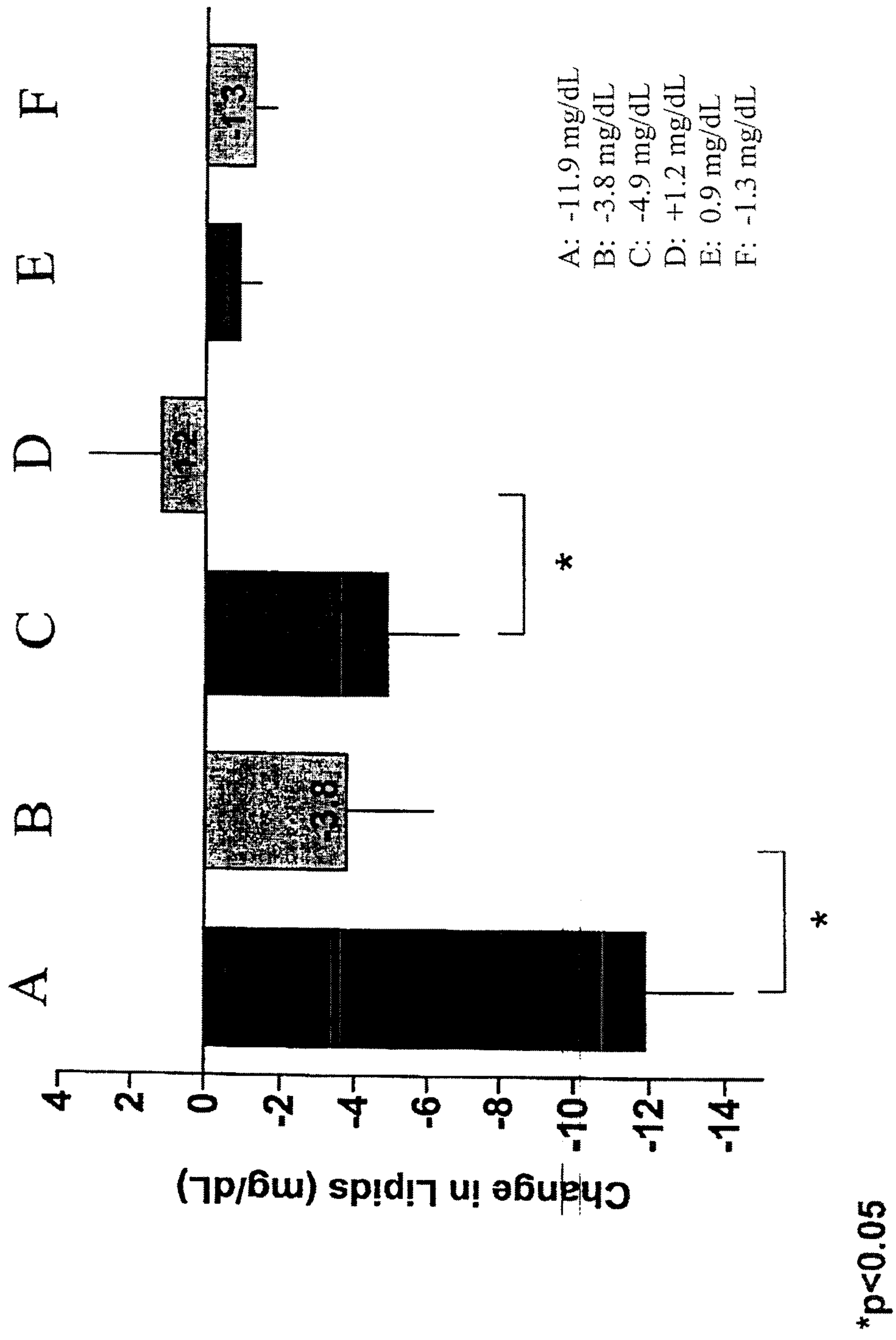

A
B
C
D
E
F
-3.8
+1.2
-1.3
*
*
A: -11.9 mg/dL
B: -3.8 mg/dL
C: -4.9 mg/dL
D: +1.2 mg/dL
E: 0.9 mg/dL
F: -1.3 mg/dL
4
2
0
-2
-4
-6
-8
-10
-12
-14
Change in Lipids (mg/dL)
*p<0.05

Figure 4

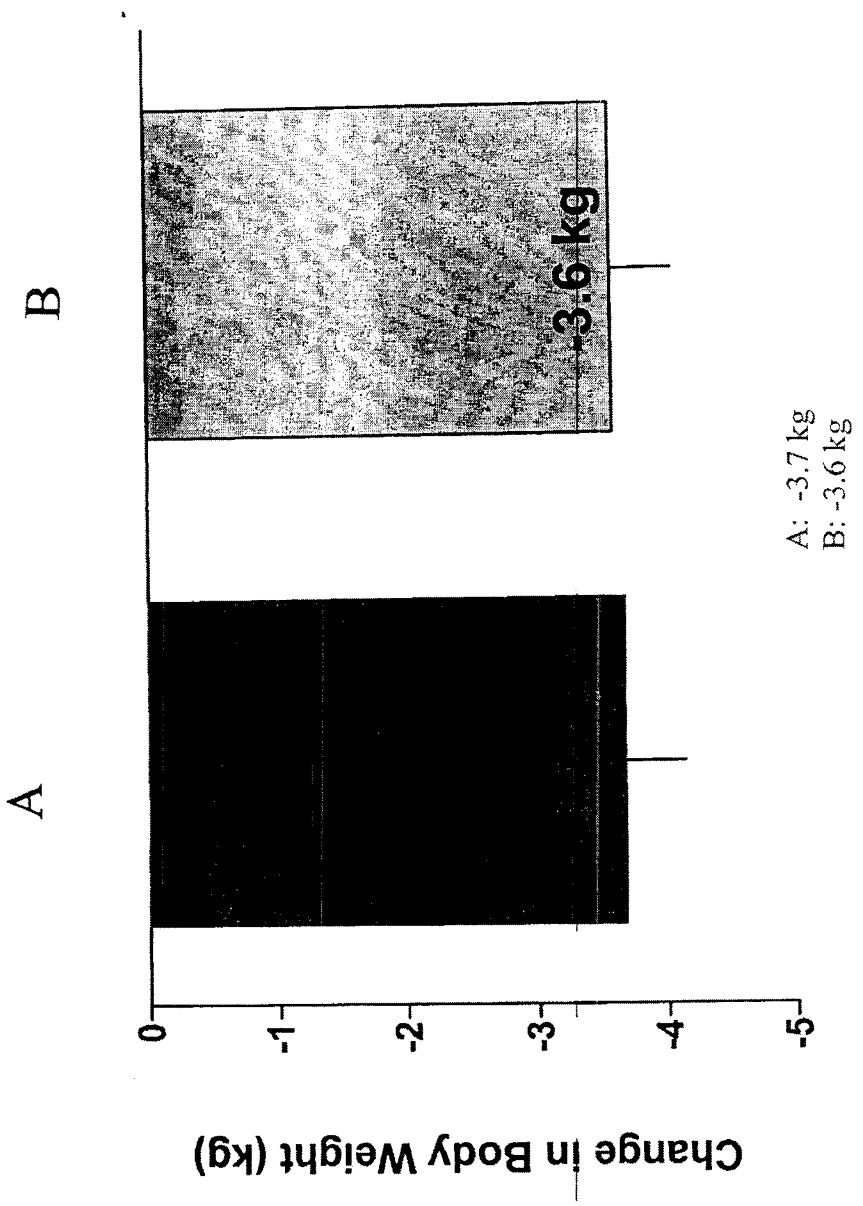


Figure 5

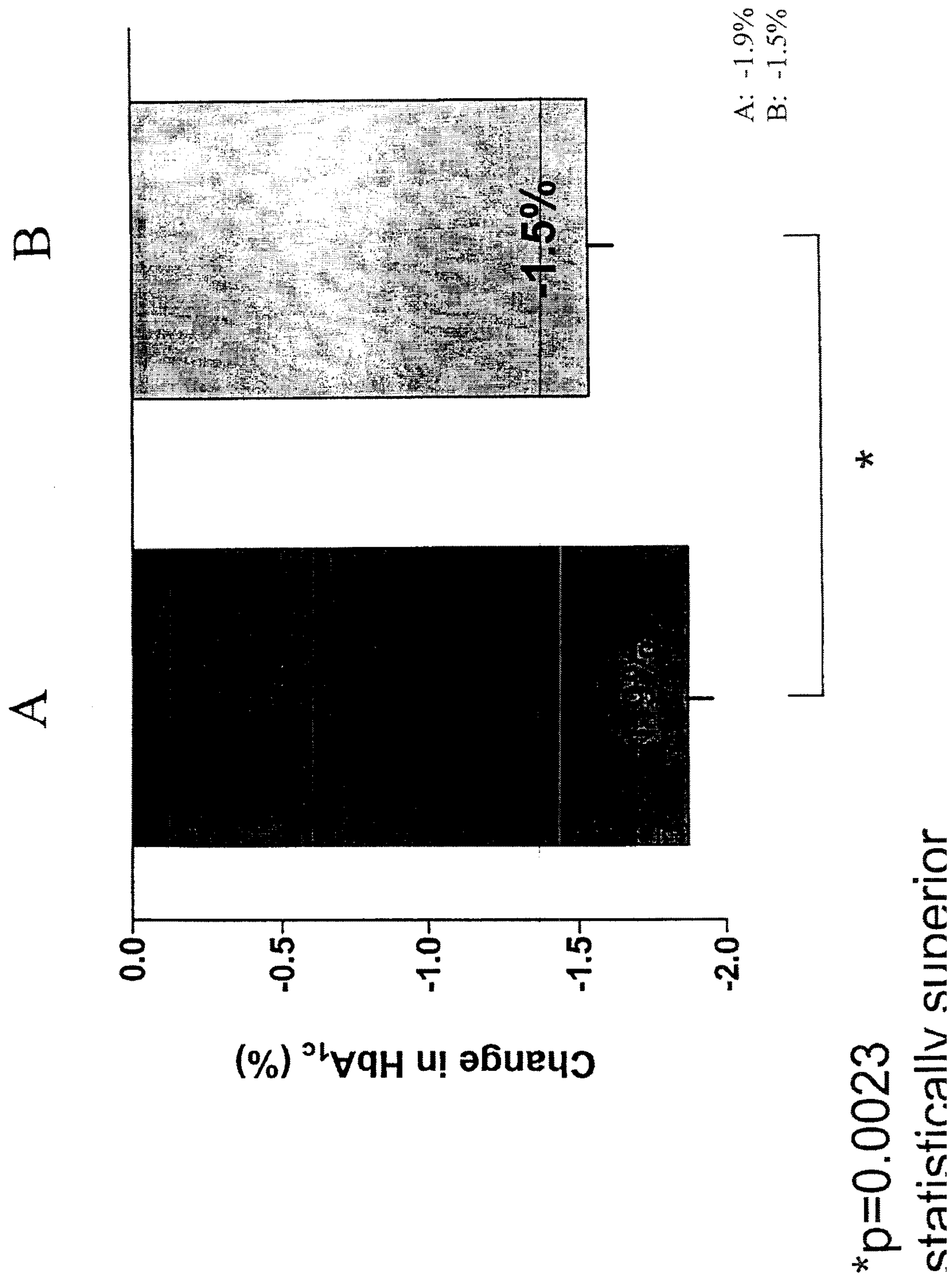
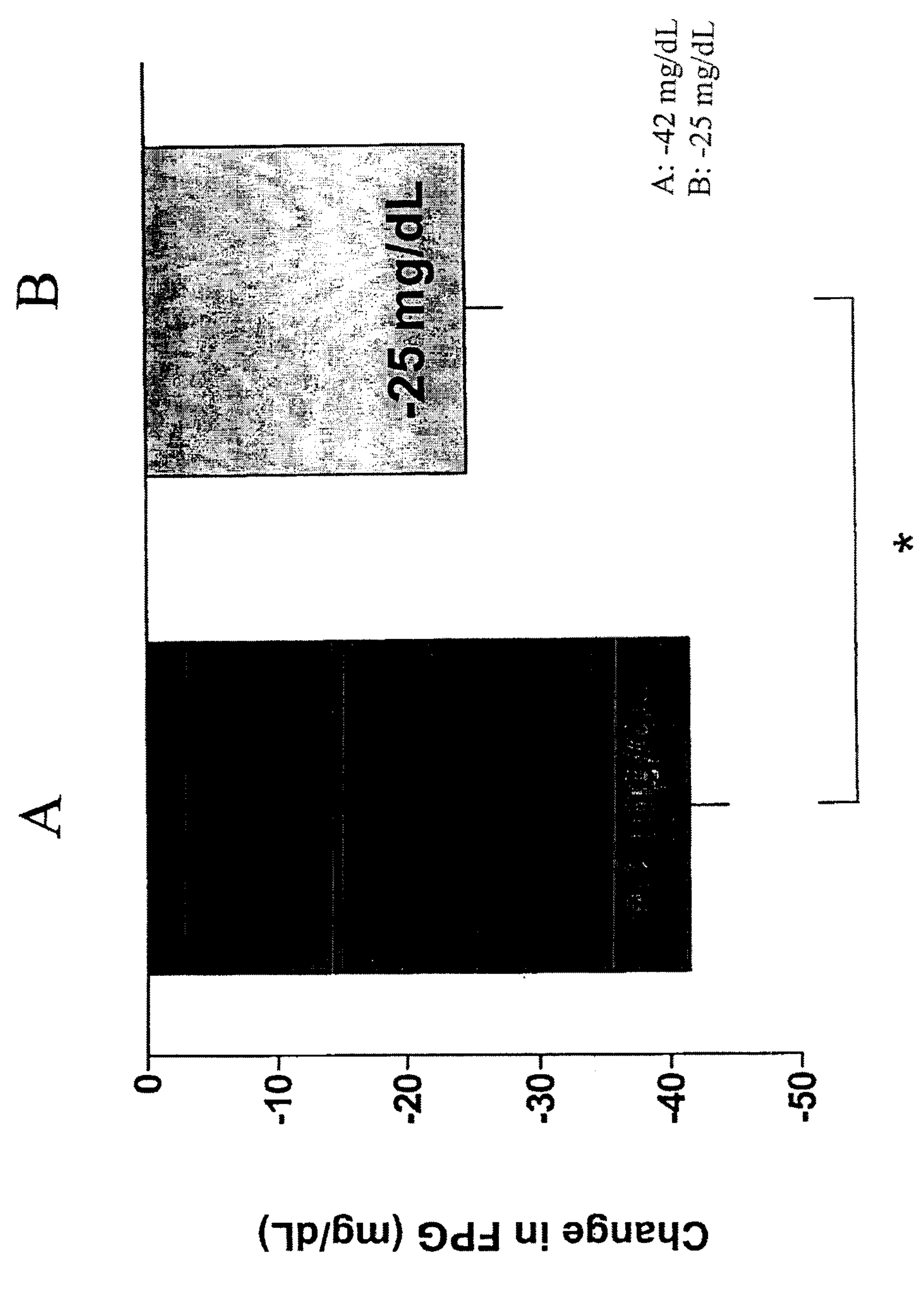

A
B
-1.5%
0.0
-0.5
-1.0
-1.5
-2.0
Change in HbA$_{1c}$ (%)
*
A: -1.9%
B: -1.5%
*p=0.0023
statistically superior

Figure 6



*p<0.0001