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(54) **Title:** DOSAGES OF GIP/GLP-1 CO-AGONIST PEPTIDES FOR HUMAN ADMINISTRATION

(57) **Abstract:** Provided herein are methods of treating obesity or diabetes, as well as related methods of reducing weight gain or inducing weight loss, treating hyperglycemia, or improving glycemic control in humans treated with a dose range of a GIP/GLP-1 co-agonist peptide.

DOSAGES OF GIP/GLP-1 CO-AGONIST PEPTIDES FOR HUMAN ADMINISTRATION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of Provisional U.S. Patent Application No. 61/875,686, filed on September 9, 2013, which is incorporated by reference in its entirety.

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 4,000 byte ASCII (Text) file named "47965A_SEQ_LIST.txt," created on September 3, 2014.

BACKGROUND

[0003] Diabetes mellitus type II (i.e., type 2 diabetes) is a heterogeneous group of conditions that constitute approximately 90% of diabetes in the United States. Type 2 diabetes is caused by a combination of insulin resistance and diminished insulin secretion. Weight reduction in obese patients is associated with improvement of insulin resistance and amelioration of diabetes symptoms.

[0004] There are five widely recognized classes of oral anti-diabetic agents, sulfonylureas, biguanides, meglitinides, thiazolidinediones, and alpha-glucosidase inhibitors. Treatment of type 2 diabetes usually involves choosing one or more of these oral agents as initial therapy (see, e.g., Charpentier G. *Diabetes Metab. Res. Rev.* 18(Supp. 3):S70-S76 (2002)). Despite the use of multiple drugs, however, the all-over control of diabetes remains inadequate. Only 49.8% of persons with diabetes achieve the National Diabetes Association target HbA_{1c} of less than 7%. Instead, 29.7% of persons with diabetes have an HbA_{1c} of greater than 8% (see, e.g., Resnick et al., *Diabetes Care* 29:531-537 (2006)).

[0005] The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), are naturally-occurring peptide hormones. Both GLP-1 and GIP stimulate insulin synthesis and secretion in a glucose-dependent manner and do not produce hypoglycemia (see, e.g., Nauck et al., *J. Clin. Endocrinol. Metab.* 76:912-917 (1993) and Irwin et al., *Regul. Pept.* 153:70-76 (2009)).

[0006] GLP-1 has been shown to be effective as adjunctive therapy for diabetes. Although GLP-1 therapy is associated with weight loss, it is also associated with nausea, which occurs in over 20% of patients that are treated with GLP-1 analogs.

[0007] Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is administered by injection once daily, at a dose of 1.2 mg or 1.8 mg. It is an analog of the human GLP-1 peptide, wherein arginine is substituted for lysine at position 34 and a 16-carbon (C16) fatty acid is attached with a glutamic acid spacer to the lysine residue at position 26.

SUMMARY

[0008] The invention provides methods for administering a peptide comprising or consisting of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, to adult humans in need thereof. Such methods are used, for example, to improve or achieve glycemic control, reduce glycemic excursions, improve glucose tolerance, reduce glucose intolerance, treat (reduce) hyperglycemia, treat type 2 diabetes, preserve pancreatic beta-cell function, increase pancreatic beta-cell function, treat insulin resistance, exert an insulinotropic effect, treat (reduce) adiposity, normalize body fat distribution, treat (reduce) dyslipidemia, prevent weight gain, reduce weight gain, reduce food intake, reduce appetite, induce weight loss, treat obesity, treat fatty liver disease, such as non-alcoholic steatohepatitis (NASH) and/or treat metabolic syndrome. Such methods are characterized by administering to the adult human a peptide comprising or consisting of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a dose ranging from about 0.75 to about 2.5 mg per day, or from about 1 to about 2 mg per day, or about 1.8 mg per day, or about 1.5 mg per day, or about 1.2 mg per day. Preferably the administration is once daily, and may be given in the morning. Administration routes include by parenteral injection or infusion, e.g. by subcutaneous administration.

[0009] SEQ ID NO: 2 and examples of peptides comprising SEQ ID NO: 2 are set out in the section entitled "*Peptide to be administered*". SEQ ID NO: 2 includes a fatty acyl group covalently attached to the peptide sequence. SEQ ID NOs: 3, 4, 5, 6, 7 and 8 are examples of peptide embodiments encompassed within SEQ ID NO: 2, with varying lengths of fatty acyl groups. It is understood that all references herein to "peptide" and uses or doses thereof includes the peptide or a pharmaceutically acceptable salt thereof.

[0010] It is understood that the invention includes corresponding uses of the peptide comprising or consisting of SEQ ID NO: 2 (e.g., SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8), or a pharmaceutically acceptable salt thereof, including uses in preparation of or packaging of a medicament for use in the methods described herein, as well as corresponding containers, packages and kits. Thus, the invention includes a peptide comprising or consisting of SEQ ID NO: 2 (e.g., SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8), or a pharmaceutically acceptable salt thereof, for use in adult humans in need thereof, at a dose ranging from about 1 to about 2.5 mg per day. Similarly, the invention includes use of a peptide comprising or consisting of SEQ ID NO: 2 (e.g., SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8), or a pharmaceutically acceptable salt thereof, in preparation of a medicament for use in adult humans in need thereof, at a dose ranging from about 1 to about 2.5 mg per day. It is understood that any of the aspects or embodiments or examples described herein with respect to methods of treatment apply equally to the “peptide for use” in such methods and to use of the peptide for treatment and in manufacture of a medicament for such methods. Such example uses are also further described below.

[0011] Accordingly, in some aspects, the invention provides methods for reducing weight gain or inducing weight loss, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg.

[0012] In related aspects, the invention provides methods of treating obesity, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg.

[0013] In some aspects, the invention provides methods of treating hyperglycemia, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg.

[0014] In related aspects, the invention provides methods of improving or achieving glycemic control, comprising administering to an adult human a peptide comprising the amino acid

sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg.

[0015] In related aspects, the invention additionally provides methods of treating diabetes, particularly type 2 diabetes, optionally non-insulin dependent or insulin dependent, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg.

[0016] In related aspects, the invention additionally provides methods of treating NASH, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg.

[0017] In any of the methods described herein, the peptide is administered in combination with a second anti-diabetic or anti-obesity agent. For example, the peptide is administered in combination with a biguanide, sulfonylurea, thiazolidinedione, gliptin, gliflozin, SGLT inhibitor, or a combination thereof. Metformin is a specific example of a commonly prescribed biguanide. In exemplary embodiments, the peptide comprising SEQ ID NO: 2 is administered in combination with metformin and a sulphonylurea. In exemplary embodiments, the peptide comprising SEQ ID NO: 2 is administered in combination with metformin and a thiazolidinedione. In exemplary embodiments, the peptide comprising SEQ ID NO: 2 is administered in combination with metformin and a gliptin. In exemplary embodiments, the peptide comprising SEQ ID NO: 2 is administered in combination with metformin and a gliflozin. In exemplary embodiments, the peptide comprising SEQ ID NO: 2 is administered in combination with metformin and a SGLT inhibitor. Examples of such therapies are described in the section entitled "*Combinations*".

[0018] Accordingly, the invention also provides methods of treating diabetes, particularly type 2 diabetes, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg, and administering, concurrently, a second therapeutic agent, such as metformin. For example, the invention also provides methods of treating Type 2 diabetic patients treated with a stable dose of metformin, comprising

administering a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, e.g., 1.8 mg. It is understood that corresponding uses include use of the peptide in preparation of a medicament for administration with metformin, and use of metformin in preparation of a medicament for administration with the peptide.

[0019] The invention also provides methods of improving or achieving glycemic control, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg, and administering, concurrently, a second therapeutic agent, such as metformin. For example, the invention also provides methods of achieving glycemic control, comprising administering a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, e.g., 1.8 mg. It is understood that corresponding uses include use of the peptide in preparation of a medicament for administration with metformin, and use of metformin in preparation of a medicament for administration with the peptide.

[0020] The invention also provides methods of treating obesity, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg, and administering, concurrently, a second therapeutic agent, such as metformin. For example, the invention also provides methods of treating obesity, comprising administering a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, e.g., 1.8 mg. It is understood that corresponding uses include use of the peptide in preparation of a medicament for administration with metformin, and use of metformin in preparation of a medicament for administration with the peptide.

[0021] Accordingly, the invention also provides methods of treating NASH, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg, and administering, concurrently, a second therapeutic agent, such as metformin. For example, the invention also provides methods of treating NASH,

comprising administering a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, e.g., 1.8 mg. It is understood that corresponding uses include use of the peptide in preparation of a medicament for administration with metformin, and use of metformin in preparation of a medicament for administration with the peptide.

[0022] Single unit doses of a peptide comprising the amino acid sequence of SEQ ID NO: 2, (e.g., SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8) or a pharmaceutically acceptable salt thereof, are also provided by the invention. In exemplary embodiments, the single unit dose comprises a dosage of about 0.75 mg to about 2.5 mg of a peptide comprising the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof. In exemplary embodiments, the single unit dose comprises a dosage of about 1.0 mg to about 2.0 mg of the peptide. In further exemplary embodiments, the single unit dose comprises a dosage of about 1.8 mg of the peptide, or a dosage of about 1.5 mg of the peptide, or a dosage of about 1.2 mg of the peptide, optionally in solution or lyophilized powder form. The single unit dose may be in any type of container, including a vial or pre-filled syringe or pre-filled device, and/or in a kit. Further examples are described below under the section entitled "*Kits and Single Unit Doses.*"

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Figure 1 represents a graph of the mean change from baseline (i.e. predose on Day 1) in fasting plasma glucose (mg/dL) over time and by dose group, for patients receiving the peptide of SEQ ID NO: 6.

[0024] Figures 2A-2D are graphs of the results of meal tolerance tests for patients receiving the peptide of SEQ ID NO: 6. Figure 2A represents results at baseline; Figure 2B, results at Day 1; Figure 2C, results at Day 7; and Figure 2D, results at Day 14.

[0025] Figure 3 represents a graph of the change in blood glucose levels (mg/dL) of mice 0 and 7 days after QD injections for 7 days with a vehicle control, liraglutide (an acylated GLP-1 analog), and three peptides of SEQ ID NO: 2, (a peptide of SEQ ID NO: 5, a peptide of SEQ ID NO: 6, and a peptide of SEQ ID NO: 7), at doses of 25 or 125 nmol/kg.

[0026] Figure 4 represents a graph of the blood glucose levels (mg/dL) of mice 0 and 7 days after the first injection with a vehicle control, liraglutide (at 30 nmol/kg/day), or SEQ ID NO: 6 (at 0.3, 1, 3, 10, or 30 nmol/kg/day).

DETAILED DESCRIPTION

[0027] As used herein, the term “treat,” as well as words related thereto, do not necessarily imply 100% or complete treatment. Rather, there are varying degrees of treatment which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the methods of treating obesity or hyperglycemia or diabetes of the invention can provide any amount or any level of treatment. Furthermore, the treatment provided by the method of the invention may include treatment of one or more conditions or symptoms or signs of the obesity or hyperglycemia or diabetes, being treated. Also, the treatment provided by the methods of the invention may encompass slowing the progression of the obesity or hyperglycemia or diabetes. For example, the methods can treat obesity by virtue of reducing weight gain, inducing weight loss, reducing food intake, and the like. For example, the methods can treat hyperglycemia or diabetes by reducing blood glucose levels, or normalizing blood glucose levels, or improving or achieving glycemic control, or reducing glycemic excursions, or improving glucose tolerance (reducing glucose intolerance) or improving insulin resistance, preserving pancreatic beta-cell function, increasing pancreatic beta-cell function, exerting an insulinotropic effect and the like. Accordingly, the invention also provides methods of reducing weight gain or inducing weight loss, reducing blood glucose levels, normalizing blood glucose levels. The invention furthermore provides methods of normalizing body fat distribution, reducing food intake, reducing appetite, and the like.

[0028] In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide

comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily. Any of these methods described herein can be applied to any of the peptide sequences encompassed by SEQ ID NO: 2, including any one of SEQ ID NOs: 3, 4, 5, 6, 7 or 8.

[0029] In exemplary aspects, the methods of the invention reduce complications associated with obesity, including but not limited to vascular disease (coronary artery disease, myocardial infarction, cerebral vascular disease stroke, peripheral vascular disease, ischemia reperfusion, etc.), hypertension, onset of diabetes type II, hyperlipidemia, dyslipidemia, nephropathy and/or musculoskeletal diseases. Accordingly, in exemplary aspects, the invention provides methods of preventing or delaying the onset of or reducing the risk of complications associated with obesity. In exemplary aspects, the invention provides a method of preventing vascular disease (coronary artery disease, myocardial infarction, cerebral vascular disease, stroke, peripheral vascular disease, ischemia reperfusion, etc.), hypertension, diabetes type II, hyperlipidemia, dyslipidemia and/or musculoskeletal diseases. In exemplary aspects, the invention provides a method of delaying the onset of vascular disease (coronary artery disease, myocardial infarction, cerebral vascular disease, stroke, peripheral vascular disease, ischemia reperfusion, etc.), hypertension, diabetes type II, hyperlipidemia, dyslipidemia and/or musculoskeletal diseases. In exemplary aspects, the invention provides a method of reducing the risk for vascular disease (coronary artery disease, myocardial infarction, cerebral vascular disease, stroke, peripheral vascular disease, ischemia reperfusion, etc.), hypertension, diabetes type II, hyperlipidemia, dyslipidemia and/or musculoskeletal diseases.

[0030] In exemplary aspects, the methods of the invention treat obesity-induced nephropathy. The method comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting

essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0031] In exemplary aspects, the adult human being treated has or suffers from vascular disease (e.g., coronary artery disease, myocardial infarction, cerebral vascular disease, stroke, peripheral vascular disease, ischemia reperfusion, etc.), hypertension, onset of diabetes type II, hyperlipidemia or dyslipidemia. In exemplary aspects, the adult human being treated has or suffers from other risk factors for cardiovascular disease, such as patients with insulin resistance or diabetes type II, hypertension, hyperlipidemia, or combinations of these risk factors. In exemplary aspects, the adult human in need thereof has or suffers from a drug-induced obesity.

[0032] In exemplary aspects, the diabetes being treated by the methods of the invention is diabetes mellitus type I, diabetes mellitus type II, or gestational diabetes, any of which may be insulin-dependent or non-insulin-dependent.

[0033] Furthermore, the treatment provided by the method of the invention may include treatment of one or more conditions or symptoms or signs of diabetes being treated.

[0034] In exemplary aspects, the methods of the invention cause an increase in insulin level, a decrease in glucose level, an increase in C-peptide level, a decrease in HbA_{1c} level, a decrease in fructosamine level, and combinations thereof. An increase in insulin level would indicate that administration of the peptide effectively is treating diabetes; and a decrease in glucose level would indicate that administration of the peptide is acting to reduce the levels of blood sugar, e.g., treating hyperglycemia.

[0035] HbA_{1c} levels depend on blood glucose concentration (i.e., the higher the glucose concentration in blood, the higher the level of HbA_{1c}), but are not influenced by daily fluctuations in the blood glucose concentration. Instead, they represent the average blood glucose level of approximately the past 4 weeks, strongly weighted toward the most recent 2 weeks. A decrease in HbA_{1c} level would indicate that administration of peptide is reducing the average blood glucose level over the long term.

[0036] C-peptide serves as a linker between the A- and B- chains of insulin and facilitates the efficient assembly, folding, and processing of insulin in the endoplasmic reticulum. High levels

of C-peptide generally indicate high levels of endogenous insulin production, while low levels of C-peptide generally indicate low levels of insulin production. An increase in C-peptide level indicates that administration of the peptide is increasing the producing of insulin.

[0037] Fructosamine can be used to identify the plasma glucose concentration. In general, the higher the fructosamine concentration, the higher the average blood glucose level. Normal fructosamine levels may indicate that a patient is either not diabetic or that the patient has good diabetic control. An increase in fructosamine levels indicates that the patient's average glucose over the last 2 to 3 weeks has been elevated. A decrease in fructosamine level would indicate that administration of the peptide is reducing the average blood glucose level.

[0038] In related aspects, the invention provides methods of improving or achieving glycemetic control, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg. In exemplary aspects, the method comprises administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0039] In related aspects, the invention provides methods of treating diabetic nephropathy, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg. In exemplary aspects, the method comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically

acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0040] In related aspects, the invention provides methods of diabetic retinopathy, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg. In exemplary aspects, the method comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0041] *Metabolic Syndrome*

[0042] In exemplary embodiments, the adult human has or suffers from metabolic syndrome. Metabolic Syndrome, also known as metabolic syndrome X, insulin resistance syndrome, or Reaven's syndrome, is a disorder that affects over 50 million Americans. Metabolic Syndrome is typically characterized by a clustering of at least three or more of the following risk factors: (1) abdominal obesity (excessive fat tissue in and around the abdomen), (2) atherogenic

dyslipidemia (blood fat disorders including high triglycerides, low HDL cholesterol and high LDL cholesterol that enhance the accumulation of plaque in the artery walls), (3) elevated blood pressure, (4) insulin resistance or glucose intolerance, (5) prothrombotic state (e.g. high fibrinogen or plasminogen activator inhibitor-1 in blood), and (6) pro-inflammatory state (e.g. elevated C-reactive protein in blood). Other risk factors may include aging, hormonal imbalance and genetic predisposition.

[0043] Metabolic Syndrome is associated with an increased risk of coronary heart disease and other disorders related to the accumulation of vascular plaque, such as stroke and peripheral vascular disease, referred to as atherosclerotic cardiovascular disease (ASCVD). Patients with metabolic syndrome may progress from an insulin resistant state in its early stages to full blown type II diabetes with further increasing risk of ASCVD. Without intending to be bound by any particular theory, the relationship between insulin resistance, metabolic syndrome and vascular disease may involve one or more concurrent pathogenic mechanisms including impaired insulin-stimulated vasodilation, insulin resistance-associated reduction in nitric oxide (NO) availability due to enhanced oxidative stress, and abnormalities in adipocyte-derived hormones such as adiponectin (Lteif and Mather, *Can. J. Cardiol.* 20 (suppl. B):66B-76B (2004)).

[0044] According to the 2001 National Cholesterol Education Program Adult Treatment Panel (ATP III), any three of the following traits in the same individual meet the criteria for metabolic syndrome: (a) abdominal obesity (a waist circumference over 102 cm in men and over 88 cm in women); (b) serum triglycerides (150 mg/dL or above); (c) HDL cholesterol (40 mg/dL or lower in men and 50 mg/dL or lower in women); (d) blood pressure (130/85 or more); and (e) fasting blood glucose (110 mg/dL or above). According to the World Health Organization (WHO), an individual having high insulin levels (an elevated fasting blood glucose or an elevated post meal glucose alone) with at least two of the following criteria meets the criteria for metabolic syndrome: (a) abdominal obesity (waist to hip ratio of greater than 0.9, a body mass index of at least 30 kg/m², or a waist measurement over 37 inches); (b) cholesterol panel showing a triglyceride level of at least 150 mg/dL or an HDL cholesterol lower than 35 mg/dL; (c) blood pressure of 140/90 or more, or on treatment for high blood pressure). (Mathur, Ruchi, "Metabolic Syndrome," ed. Shiel, Jr., William C., *MedicineNet.com*, May 11, 2009).

[0045] For purposes herein, if an individual meets the criteria of either or both of the criteria set forth by the 2001 National Cholesterol Education Program Adult Treatment Panel or the WHO, that individual is considered as afflicted with metabolic syndrome. In exemplary aspects, the adult human meets the criteria of either or both of the criteria set forth by the 2001 National Cholesterol Education Program Adult Treatment Panel or the WHO, that individual is considered as afflicted with metabolic syndrome.

[0046] In exemplary aspects, the adult human does not meet either of the above criteria for metabolic syndrome, but the adult human meets some (e.g., one or two or three) of the criteria as set forth by the 2001 National Cholesterol Education Program Adult Treatment Panel or the WHO.

[0047] *Non-Alcoholic Fatty Liver Disease*

[0048] The invention also provides methods of treating an adult human with nonalcoholic fatty liver disease (NAFLD) or alcoholic liver disease, or alcohol-induced liver disease, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg. In exemplary aspects, the method comprises administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0049] The NAFLD or alcoholic liver disease, or alcohol-induced liver disease may be present at any stage. NAFLD refers to a wide spectrum of liver disease ranging from simple fatty liver (steatosis), to nonalcoholic steatohepatitis (NASH), to cirrhosis (irreversible, advanced scarring

of the liver). All of the stages of NAFLD have in common the accumulation of fat (fatty infiltration) in the liver cells (hepatocytes). Simple fatty liver is the abnormal accumulation of a certain type of fat (e.g., triglyceride) in the liver cells with no inflammation or scarring. In NASH, the fat accumulation is associated with varying degrees of inflammation (hepatitis) and scarring (fibrosis) of the liver. The inflammatory cells can destroy the liver cells (hepatocellular necrosis). In the terms "steatohepatitis" and "steatonecrosis", steato refers to fatty infiltration, hepatitis refers to inflammation in the liver, and necrosis refers to destroyed liver cells. NASH can ultimately lead to scarring of the liver (fibrosis) and then irreversible, advanced scarring (cirrhosis). Cirrhosis that is caused by NASH is the last and most severe stage in the NAFLD spectrum. (Mendler, Michel, "Fatty Liver: Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)," ed. Schoenfield, Leslie J., MedicineNet.com, August 29, 2005).

[0050] Alcoholic liver disease encompasses three pathologically distinct liver diseases related to, or caused by, the excessive consumption of alcohol: fatty liver (steatosis), chronic or acute hepatitis, and cirrhosis. Alcoholic hepatitis can range from a mild hepatitis, with abnormal laboratory tests being the only indication of disease, to severe liver dysfunction with complications such as jaundice (yellow skin caused by bilirubin retention), hepatic encephalopathy (neurological dysfunction caused by liver failure), ascites (fluid accumulation in the abdomen), bleeding esophageal varices (varicose veins in the esophagus), abnormal blood clotting and coma. Histologically, alcoholic hepatitis has a characteristic appearance with ballooning degeneration of hepatocytes, inflammation with neutrophils and sometimes Mallory bodies (abnormal aggregations of cellular intermediate filament proteins). Cirrhosis is characterized anatomically by widespread nodules in the liver combined with fibrosis. (Worman, Howard J., "Alcoholic Liver Disease", Columbia University Medical Center website).

[0051] The treatment methods in this embodiment of the invention may result in reduction in one, two, three or more of the following: liver fat content, incidence or progression of cirrhosis, incidence of hepatocellular carcinoma, signs of inflammation, such as abnormal hepatic enzyme levels (e.g., aspartate aminotransferase AST and/or alanine aminotransferase ALT, or LDH), elevated serum ferritin, elevated serum bilirubin, and/or signs of fibrosis, e.g. elevated TGF-beta levels. In preferred embodiments, the peptide is used to treat patients who have progressed

beyond simple fatty liver (steatosis) and exhibit signs of inflammation or hepatitis. Such methods may result, for example, in reduction of AST and/or ALT levels.

[0052] *Alzheimer's disease*

[0053] Alzheimer's disease (AD), also known as Alzheimer disease, is the most common form of dementia. AD is most often diagnosed in people over 65 years of age. However, early-onset AD can be diagnosed in people younger than 65 years. Common symptoms in AD include, but are not limited to, difficulty in remembering recent events, confusion, irritability, aggression, mood swings, trouble with language, and long-term memory loss. During the early stages of AD, impairment of learning and memory may lead to the diagnosis of AD. Additional symptoms include difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia). During the middle stages, progressive deterioration eventually hinders independence, with subjects being unable to perform most common activities of daily living (Forstl, *Eur. Archives of Psychiatry and Clin Neurosci* 249(6): 288-290 (1999)). Difficulties in speech become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions (paraphasias). Reading and writing skills are progressively lost (Forstl (1999), *supra*, Frank, *J S C Med Assoc* 90(9): 417-423 (1994)). Complex motor sequences become less coordinated as AD progresses. Consequently, the risk of falling increases (Forstl (1999), *supra*). During this phase, memory problems worsen, and the person may fail to recognize close relatives (Forstl (1999), *supra*). Long-term memory becomes impaired (Forstl (1999), *supra*).

[0054] Behavioural and neuropsychiatric changes become more prevalent and common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving (Forstl (1999), *supra*). Sundowning also may appear (Volicer et al., *Am J Psychiatry* 158(5): 704-711 (2001)). Approximately 30% of people with AD develop illusionary misidentifications and other delusional symptoms (Forstl (1999), *supra*). Subjects also lose insight of their disease process and limitations (anosognosia) and urinary incontinence can develop (Forstl (1999), *supra*).

[0055] During the late or advanced stages, a person with AD is completely dependent upon a caregiver. Language is reduced to simple phrases or even single words and eventually leads to complete loss of speech (Forstl (1999), *supra*). People can often understand and return

emotional signals, despite the loss of verbal language abilities (Forstl (1999), *supra*). Although aggressiveness can still be present, extreme apathy and exhaustion are much more common results (Forstl (1999), *supra*). People with AD ultimately will not be able to perform even the simplest tasks without assistance (Forstl (1999), *supra*). Muscle mass and mobility deteriorate to the point where they are bedridden, and they lose the ability to feed themselves (Forstl (1999), *supra*). AD is a terminal illness, with the cause of death typically being an external factor, such as infection of pressure ulcers or pneumonia, not the disease itself (Forstl (1999), *supra*).

[0056] The invention also provides methods of treating an adult human for Alzheimer's disease, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg. In exemplary aspects, the method comprises administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0057] *Parkinson's disease (PD)*

[0058] PD, also known as idiopathic or primary parkinsonism, hypokinetic rigid syndrome/HRS, or paralysis agitans) is a degenerative disorder of the central nervous system. During the early stages, the most obvious symptoms are movement-related, including shaking, rigidity, slowness of movement and difficulty with walking and gait. During the later stages of PD, thinking and behavioral problems arise, with dementia commonly occurring in the advanced stages of the disease, and depression is the most common psychiatric symptom. Additional

symptoms include sensory, sleep and emotional problems. Parkinson's disease is more common in older people and most cases occurring after the age of 50.

[0059] The invention also provides methods of treating an adult human for Parkinson's disease, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg. In exemplary aspects, the method comprises administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0060] *Prader Willi Syndrome*

[0061] Prader Willi Syndrome (PWS) is a rare, genetic disorder. In PWS, seven genes on chromosome 15 (q11-13) are deleted or unexpressed on the paternal chromosome. PWS is characterized by "low muscle tone, short stature, incomplete sexual development, cognitive disabilities, problem behaviors, and a chronic feeling of hunger that can lead to excessive eating and life-threatening obesity" "Questions and Answers on Prader Willi Syndrome," *Prader-Willi Syndrome Association*. Retrieved February 2, 2012. The incidence of PWS is between 1 in 25,000 and 1 in 10,000 live births. The signs and symptoms of PWS vary from poor muscle tone to behavioral problems. A lack of eye coordination, a weak sucking reflex, weak cry, difficulty waking up are symptoms of PWS. PWS is often associated with an extreme and insatiable appetite, often resulting in morbid obesity. It is the most common genetic cause of morbid obesity in children (Nordqvist, *Medical News Today*, MediLexicon International, Retrieved

December 4, 2012). Individuals with PWS are at risk of learning and attention difficulties with 39% of PWS subjects having and IQ of 50-70.

[0062] The invention also provides methods of treating an adult human for Prader Willi Syndrome, comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg, or about 1.8 mg. In exemplary aspects, the method comprises administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of any one of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.5 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of from about 0.75 mg to about 2.0 mg, or about 1.0 mg to about 2.0 mg. In exemplary aspects, these methods comprise administering to an adult human in need thereof a peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, at a daily dosage of about 1.8 mg, or about 1.5 mg. Preferably the peptide is administered once daily.

[0063] *Peptide to be administered*

[0064] In relation to the various aspects of the invention, including methods, uses, single unit doses and kits, the peptide comprises, consists essentially of, or consists of the amino acid sequence of SEQ ID NO: 2, which is set out below:

Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Tyr Leu Asp Lys Gln Ala Ala Xaa Glu Phe
Val Asn Trp Leu Leu Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Lys

wherein Xaa at position 2 is 2-aminoisobutyric acid or alpha-aminoisobutyric acid (AIB);

wherein Xaa at position 20 is 2-aminoisobutyric acid or alpha-aminoisobutyric acid (AIB);

wherein the Lys at position 40 of which is covalently attached to a fatty acyl group; and

wherein the C-terminus is amidated;

(SEQ ID NO: 2).

[0065] Such peptides have been tested and observed to exhibit agonist activity at both the GLP-1 receptor and the GIP receptor.

[0066] In exemplary aspects, the peptide consists essentially of the amino acid sequence of SEQ ID NO: 2.

[0067] In exemplary aspects, the peptide consists of the amino acid sequence of SEQ ID NO: 2.

[0068] It is understood that all references to “peptide” herein include any pharmaceutically acceptable salts of the peptide. Example salts are described below under the section entitled “*Salts.*”

[0069] In exemplary aspects, the fatty acyl group attached to the Lys at position 40 of the peptide is a 4-carbon to 30-carbon fatty acyl group. For example, the fatty acyl group is a 4-carbon fatty acyl group, 6-carbon fatty acyl group, 8-carbon fatty acyl group, 10-carbon fatty acyl group, 12-carbon fatty acyl group, 14-carbon fatty acyl group, 16-carbon fatty acyl group, 18-carbon fatty acyl group, 20-carbon fatty acyl group, 22-carbon fatty acyl group, 24-carbon fatty acyl group, 26-carbon fatty acyl group, 28-carbon fatty acyl group, or a 30-carbon fatty acyl group. In exemplary aspects, the fatty acyl group is a 8-carbon to 20-carbon fatty acyl group or a 12-carbon to 20-carbon fatty acyl group, or a 14-carbon to 18-carbon fatty acyl group. In exemplary aspects, the fatty acyl group is a 14-carbon fatty acyl group, a 16-carbon fatty acyl group, or an 18-carbon fatty acyl group. In exemplary aspects, fatty acyl group is linear or branched.

[0070] Accordingly, in exemplary aspects, the peptide comprises the amino acid sequence of SEQ ID NO: 2, wherein the Lys at position 40 of which is covalently attached to a C12-C20 fatty acyl group (e.g., a 12-carbon fatty acyl group, a 14-carbon fatty acyl group, 16-carbon fatty acyl group, 18-carbon fatty acyl group, 20-carbon fatty acyl group), as described in SEQ ID NO: 3. In exemplary aspects, the peptide comprises the amino acid sequence of SEQ ID NO: 2, wherein the Lys at position 40 of which is covalently attached to 12-carbon (C12) fatty acyl group, as described in SEQ ID NO: 4. In exemplary aspects, the peptide comprises the amino acid sequence of SEQ ID NO: 2, wherein the Lys at position 40 of which is covalently attached to 14-carbon (C14) fatty acyl group, as described in SEQ ID NO: 5. In exemplary aspects, the peptide comprises the amino acid sequence of SEQ ID NO: 2, wherein the Lys at position 40 of which is

covalently attached to 16-carbon (C16) fatty acyl group, as described in SEQ ID NO: 6. In exemplary aspects, the peptide comprises the amino acid sequence of SEQ ID NO: 2, wherein the Lys at position 40 of which is covalently attached to 18-carbon (C18) fatty acyl group, as described in SEQ ID NO: 7. In exemplary aspects, the peptide comprises the amino acid sequence of SEQ ID NO: 2, wherein the Lys at position 40 of which is covalently attached to 20-carbon (C20) fatty acyl group, as described in SEQ ID NO: 8. Accordingly, with regard to any of the methods provided herein, the method comprises administering to an adult human a peptide comprising, consisting essentially of, or consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 8.

[0071] In exemplary aspects, the peptide utilized in the methods of the invention is a peptide of SEQ ID NO: 6:

Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Tyr Leu Asp Lys Gln Ala Ala Xaa Glu Phe
Val Asn Trp Leu Leu Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Lys

wherein Xaa at position 2 is 2-aminoisobutyric acid or alpha-aminoisobutyric acid (AIB);

wherein Xaa at position 20 is 2-aminoisobutyric acid or alpha-aminoisobutyric acid (AIB);

wherein the Lys at position 40 of which is covalently attached to a 16-carbon fatty acyl group;

and wherein the C-terminus is amidated;

(SEQ ID NO: 6).

[0072] *Dosing and administration*

[0073] In exemplary embodiments of the invention, the peptide, or pharmaceutically acceptable salt thereof, is administered to the adult human at a daily dosage of about 0.75 mg to about 2.5 mg. In exemplary aspects, the peptide is administered to the adult human at a daily dosage of about 0.75 mg, about 0.80 mg, about 0.85 mg, about 0.90 mg, about 0.95 mg, about 1.0 mg, about 1.05 mg, about 1.10 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, about 1.75 mg, about 1.8 mg, about 1.85 mg, about 1.9 mg, about 1.95 mg, about 2.0 mg, about 2.05 mg, about 2.1 mg, about 2.1 mg, about 2.15 mg, about 2.2 mg, about 2.25 mg, about 2.3 mg, about 2.35 mg, about 2.4 mg, about 2.45 mg, about 2.5 mg, about 2.55 mg, about 2.6 mg, about 2.65 mg, about 2.7 mg, or about 2.75 mg. In exemplary

aspects, the peptide is administered at a daily dosage of about 0.75 mg to about 2.0 mg. In exemplary aspects, the peptide is administered at a daily dosage of about 1.0 mg to about 2.0 mg. In exemplary aspects, the peptide is administered at a daily dosage of about 1.0 mg to about 2.5 mg. In exemplary aspects, the peptide is administered at a daily dosage of about 1.2 mg to about 1.8 mg. In exemplary aspects, the peptide is administered at a daily dosage of about 1.5 to about 2.0 mg. In exemplary aspects, the peptide is administered at a daily dosage of about 1.6 to about 1.9 mg. In exemplary aspects, the peptide is administered at a daily dosage of about 1.8 mg.

[0074] Preferably, the peptide is administered to said adult human once daily. In some situations, the peptide is administered every two days, at an equivalent dose (e.g. instead of 1.8 mg every day, about 3.5 mg every two days).

[0075] *Pharmaceutical formulations and routes of administration*

[0076] In exemplary embodiments, the peptide, or pharmaceutically acceptable salt thereof, is administered to the adult human as part of a pharmaceutical composition. In exemplary aspects, the pharmaceutical composition comprises the peptide and a pharmaceutically acceptable diluent, carrier, and/or excipient. In some embodiments, the pharmaceutical composition is sterile and has a purity level of, for example, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99%.

[0077] In exemplary embodiments, the pharmaceutical composition comprises the peptide at a concentration of about 1 mg/mL to about 50 mg/mL (e.g., about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 11 mg/mL, about 12 mg/mL, about 13 mg/mL, about 14 mg/mL, about 15 mg/mL, about 16 mg/mL, about 17 mg/mL, about 18 mg/mL, about 19 mg/mL, about 20 mg/mL, about 21 mg/mL, about 22 mg/mL, about 23 mg/mL, about 24 mg/mL, about 25 mg/mL, about 26 mg/mL, about 27 mg/mL, about 28 mg/mL, about 29 mg/mL, about 30 mg/mL, about 31 mg/mL, about 32 mg/mL, about 33 mg/mL, about 34 mg/mL, about 35 mg/mL, about 36 mg/mL, about 37 mg/mL, about 38 mg/mL, about 39 mg/mL, about 40 mg/mL, about 41 mg/mL, about 42 mg/mL, about 43 mg/mL, about 44 mg/mL, about 45 mg/mL, about 46 mg/mL, about 47 mg/mL, about 48 mg/mL, about 49 mg/mL, and about 50 mg/mL).

[0078] In exemplary embodiments, the pharmaceutical composition is prepared as an aqueous solution, e.g., a sterilized aqueous solution. In exemplary aspects, the pharmaceutical composition is stored in a container, such as any of those described herein. See, e.g., the section entitled “*Kits and Single Unit Doses.*” In some embodiments, the pharmaceutical composition is prepared as a pre-formulated solution ready for injection. In exemplary embodiments the pharmaceutical composition is prepared as a lyophilized powder.

[0079] Standard routes of administration are contemplated, including parenterally, such as intravenously, intraperitoneally, subcutaneously or intramuscularly, intrathecally, transdermally, rectally, orally, nasally or by inhalation. Parenteral injection or extended infusion, e.g. over a period of 10 minutes, 15 minutes, 30 minutes, 1 hour or 2 hours is possible. Subcutaneous administration is preferred.

[0080] In some embodiments, the pharmaceutical composition comprises the peptide of the present disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and/or one or more pharmaceutically acceptable ingredients. Remington’s Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), which is incorporated by reference in its entirety, discloses various components used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional agent is incompatible with the pharmaceutical compositions, its use in pharmaceutical compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

[0081] In some embodiments, the pharmaceutically acceptable ingredient is selected from the group consisting of a sugar (e.g., glucose, sucrose, trehalose, lactose, fructose, maltose, dextran, glycerin, dextran, mellibiose, melezitose, raffinose, mannotriose, stachyose, maltose, lactulose, maltulose, or iso-maltulose, or combinations of these sugars), a sugar alcohol (e.g., glycol, glycerol, erythritol, threitol, arabitol, xylitol, ribitol, mannitol, sorbitol, dulcitol, iditol, isomalt, maltitol, lactitol, or glucitol, or combinations of these sugar alcohols), a salt (e.g., sodium chloride), an emulsifier or surfactant (e.g., polysorbates, such as polyoxyethylene 20 sorbitan monooleate, or other block copolymers of ethylene oxide and propylene oxide), lyoprotectants, and mixtures thereof. For example, excipients such as sugars or sugar alcohols are present, e.g.,

in a concentration of about 20 mg/mL to about 40 mg/mL, or 25 to 45 mg/mL, such as 35 mg/mL.

[0100] The pharmaceutical composition may be formulated to achieve a physiologically compatible pH, e.g. about pH 4 to about pH 11. In some embodiments, the pH of the pharmaceutical composition is, e.g., about 7 to 10. In other embodiments, the pH of the pharmaceutical composition is, e.g., about 4 to 7, or 4.5 to about 5.5, for example, about 5.

[0101] In certain embodiments, the pharmaceutical compositions may comprise buffering agents to achieve a physiological compatible pH. The buffering agents may include any compounds capable of buffering at the desired pH such as, for example, phosphate buffers (e.g. PBS), triethanolamine, Tris, bicine, TAPS, tricine, HEPES, TES, MOPS, PIPES, cacodylate, MES, acetate, citrate, succinate, histidine or other pharmaceutically acceptable buffers. In certain embodiments, the strength of the buffer is at least 0.5 mM, at least 1 mM, at least 5 mM, at least 10 mM, at least 20 mM, at least 30 mM, at least 40 mM, at least 50 mM, at least 60 mM, at least 70 mM, at least 80 mM, at least 90 mM, at least 100 mM, at least 120 mM, at least 150 mM, or at least 200 mM. In some embodiments, the strength of the buffer is no more than 300 mM (e.g. at most 200 mM, at most 100 mM, at most 90 mM, at most 80 mM, at most 70 mM, at most 60 mM, at most 50 mM, at most 40 mM, at most 30 mM, at most 20 mM, at most 10 mM, at most 5 mM, at most 1 mM). For example, the buffer concentration can be about 2 mM to about 100 mM, or about 10 mM to about 50 mM.

[0102] Any of the pharmaceutical compositions described herein may be administered alone or in combination with another therapeutic agent.

[0103] The invention provides any of the pharmaceutical compositions described herein. In exemplary aspects, the pharmaceutical composition additionally comprises a second therapeutic agent. The second therapeutic agent may be any of those described below. See the section entitled "*Combinations*."

[0104] *Salts*

[0105] In exemplary aspects, the peptide is in the form of a salt, e.g., a pharmaceutically acceptable salt. As used herein the term "pharmaceutically acceptable salt" refers to salts of compounds that retain the biological activity of the parent compound, and which are not

biologically or otherwise undesirable. Such salts can be prepared *in situ* during the final isolation and purification of the analog, or separately prepared by reacting a free base function with a suitable acid. Many of the compounds disclosed herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0106] Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphor sulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methane sulfonate, nicotinate, 2-naphthalene sulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate, and undecanoate. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include, for example, an inorganic acid, e.g., hydrochloric acid, hydrobromic acid, sulphuric acid, and phosphoric acid, and an organic acid, e.g., oxalic acid, maleic acid, succinic acid, and citric acid.

[0107] Basic addition salts also can be prepared *in situ* during the final isolation and purification, or by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary, or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like, and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium, amongst others. Other

representative organic amines useful for the formation of base addition salts include, for example, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines.

[0108] Further, basic nitrogen-containing groups can be quaternized with the analog of the present disclosure as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

[0109] *Combinations*

[0110] In exemplary aspects, the peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, is administered alone, e.g., without any other therapeutic agent, without any other anti-diabetic agent and/or any other anti-obesity agent, including any of those listed below.

[0111] In alternative aspects, the peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof, is administered in combination with an effective amount of one or more second therapeutic agents.

[0112] In exemplary aspects, the second therapeutic agent is an anti-diabetic agent, an anti-obesity agent, or a mixture thereof. Anti-diabetic agents known in the art or under investigation include insulin, sulfonylureas, such as tolbutamide (Orinase), acetohexamide (Dymelor), tolazamide (Tolinase), chlorpropamide (Diabinese), glipizide (Glucotrol), glyburide (Diabeta, Micronase, Glynase), glimepiride (Amaryl), or gliclazide (Diamicron); meglitinides, such as repaglinide (Prandin) or nateglinide (Starlix); biguanides such as metformin (Glucophage) or phenformin; thiazolidinediones such as rosiglitazone (Avandia), pioglitazone (Actos), or troglitazone (Rezulin), or other PPAR γ inhibitors; alpha glucosidase inhibitors that inhibit carbohydrate digestion, such as miglitol (Glyset), acarbose (Precose/Glucobay); exenatide (Byetta) or pramlintide; Dipeptidyl peptidase-4 (DPP-4) inhibitors such as vildagliptin or sitagliptin; SGLT (sodium-dependent glucose transporter 1) inhibitors; glucokinase activators (GKA); glucagon receptor antagonists (GRA); or FBPase (fructose 1,6-bisphosphatase) inhibitors. For example, the peptides disclosed herein can be administered with insulin.

[0113] Anti-obesity agents known in the art or under investigation include, Leptin and Fibroblast Growth Factor 21 (FGF-21), appetite suppressants, such as phenethylamine type stimulants, phentermine (optionally with fenfluramine or dexfenfluramine), diethylpropion (Tenuate®), phendimetrazine (Prelu-2®, Bontril®), benzphetamine (Didrex®), sibutramine (Meridia®, Reductil®); rimonabant (Acomplia®), other cannabinoid receptor antagonists; oxyntomodulin; fluoxetine hydrochloride (Prozac); Qnexa (topiramate and phentermine), Excalia (bupropion and zonisamide) or Contrave (bupropion and naltrexone); or lipase inhibitors, similar to xenical (Orlistat) or Cetilistat (also known as ATL-962), or GT 389-255.

[0114] With regard to any one of the inventive methods herein, the method comprises, in some aspects, administering the peptide of any one of SEQ ID NOs: 2-8 with Metformin. In exemplary aspects, the method comprises administering the peptide of any one of SEQ ID NOs: 2-8 with Metformin to a patient with insufficient glycemic control. In exemplary aspects, the method comprises administering the peptide of any one of SEQ ID NOs: 2-8 with Metformin to a patient who has been administered the maximum tolerated dose of monotherapy with Metformin or a sulphonylurea, yet the patient still exhibits insufficient glycemic control.

[0115] In exemplary aspects, the methods comprise administering the peptide of any one of SEQ ID NOs: 2-8 with Metformin and a third therapeutic agent. In exemplary aspects, the methods comprise administering the peptide of any one of SEQ ID NOs: 2-8 with Metformin and a third therapeutic agent selected from the group consisting of: sulphonylurea, thiazolidinedione, gliptin, gliflozin. In exemplary aspects, the method comprises administering to a patient with insufficient glycemic control the peptide of any one of SEQ ID NOs: 2-8 with Metformin and a third therapeutic agent selected from the group consisting of: sulphonylurea, thiazolidinedione, gliptin, gliflozin. In exemplary aspects, the method comprises administering to a patient who has been treated with dual therapy, yet the patient still exhibits insufficient glycemic control, the peptide of any one of SEQ ID NOs: 2-8 with Metformin and a third therapeutic agent selected from the group consisting of: sulphonylurea, thiazolidinedione, gliptin, gliflozin.

Thiazolidinediones, also known as glitazones, are known in the art and include, e.g., rosiglitazone, pioglitazone, troglitazone, netoglitazone, rivoglitazone, ciglitazone. Gliptins, also known as inhibitors of dipeptidyl peptidase 4 or DPP-4 inhibitors, are known in the art, and include but not limited to, sitagliptin, vildagliptin, saxagliptin, linagliptin, dutogliptin, gemigliptin, alogliptin, anagliptin, berberine, and lupeol. Gliflozins are SGLT inhibitors (i.e.,

inhibitors of the SGLT2 glucose transporter) and include, but not limited to, dapagliflozin and sergliflozin.

[0116] With regard to any one of the inventive methods herein, the method comprises, in some aspects, administering the peptide of any one of SEQ ID NOs: 2-8 with a sulfonylurea. In exemplary aspects, the method comprises administering the peptide of any one of SEQ ID NOs: 2-8 with a sulfonylurea to a patient with insufficient glycemic control. In exemplary aspects, the method comprises administering the peptide of any one of SEQ ID NOs: 2-8 with a sulfonylurea to a patient who has been administered the maximum tolerated dose of monotherapy with Metformin or a sulphonylurea, yet the patient still exhibits insufficient glycemic control. Sulphonylureas are known in the art and include, but not limited to, carbutamide, acetohexamide, tolbutamide (Orinase), acetohexamide (Dymelor), tolazamide (Tolinase), chlorpropamide (Diabinese), glipizide (Glucotrol), glyburide (glibenclamide, Diabeta, Micronase, Glynase), glimepiride (Amaryl), gliclazide (Diamicron), glibornuride, gliquidone, glisoxepide, and glyclopamide.

[0117] *Kits and Single Unit Doses*

[0118] In exemplary embodiments, the pharmaceutical composition is packaged as part of a kit. Accordingly, the invention provides a kit comprising any of the pharmaceutical compositions comprising the peptide described herein and a device for administering the peptide to a patient, e.g., adult human. In exemplary embodiments, the pharmaceutical compositions of the kits are in the form of an aqueous solution that is sterilized. In some embodiments, the peptides are used to prepare pre-formulated solutions ready for injection. In other embodiments the pharmaceutical compositions comprise a lyophilized powder.

[0119] In exemplary aspects, the device for administering the peptide is a syringe needle, pen device, jet injector or other needle-free injector. In exemplary aspects, the device is a disposable device. In some embodiments the device of the kit is an aerosol dispensing device, wherein the peptides are prepackaged within the aerosol device. In another embodiment the kit comprises a syringe and a needle, and in one embodiment the sterile peptides are prepackaged within the syringe.

[0120] In exemplary aspects, the pharmaceutical composition is stored in one of various containers. The container in some aspects is a vial, tube, bottle, a single or multi-chambered pre-

filled syringe, cartridge, infusion pump (external or implantable), jet injector, pre-filled pen device and the like.

[0121] In exemplary aspects, the kits also include instructions for use or for storage. In exemplary aspects, the pharmaceutical composition of the kit is in the form of a lyophilized powder, and the kit comprises instructions for adding an amount of an aqueous solution to the lyophilized powder. In exemplary aspects, the kits are labeled for storage at ambient room temperature or at refrigerated temperature.

[0122] Additionally provided herein are single unit doses of peptide. In exemplary embodiments, the single unit dose comprises, consists essentially of, or consists of a dosage of about 0.75 mg to about 2.5 mg of the peptide comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO: 2, or a pharmaceutically acceptable salt thereof. In exemplary aspects, the single unit dose comprises, consists essentially of, or consists of a dosage of the peptide which is about 0.75 mg, about 0.80 mg, about 0.85 mg, about 0.90 mg, about 0.95 mg, about 1.0 mg, about 1.05 mg, about 1.10 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, about 1.75 mg, about 1.8 mg, about 1.85 mg about 1.9 mg, about 1.95 mg, about 2.0 mg, about 2.05 mg, about 2.1 mg, about 2.1 mg, about 2.15 mg, about 2.2 mg, about 2.25 mg, about 2.3 mg, about 2.35 mg, about 2.4 mg, about 2.45 mg, about 2.5 mg, about 2.55 mg, about 2.6 mg, about 2.65 mg, about 2.7 mg, or about 2.75 mg. In exemplary aspects, the single unit dose comprises, consists essentially of, or consists of a dosage of the peptide which is about 1.0 mg to about 2.0 mg. In exemplary aspects, the single unit dose comprises, consists essentially of, or consists of a dosage of the peptide which is about 1.2 to about 1.8 mg, or about 1.5 to about 2.0 mg, or about 1.6 to about 1.9 mg. In exemplary aspects, the single unit dose comprises, consists essentially of, or consists of a dosage of the peptide which is about 1.8 mg.

[0123] *Exemplary Embodiments*

[0124] In exemplary embodiments, the invention provides:

1. A method of improving glycemic control comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a

pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg.

2. The method of claim 1 wherein the adult human has type 2 diabetes, optionally non-insulin dependent or insulin dependent.

3. The method of claim 1 wherein the adult human is a type 2 diabetic patient being treated with a stable dose of metformin.

4. A method of reducing weight gain or inducing weight loss comprising administering to an adult human a peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, once daily at a dosage of about 0.75 mg to about 2.5 mg.

5. The method of claim 4 for treating obesity.

6. The method of any one of claims 1 to 5, wherein the daily dosage is about 1.0 mg to about 2.0 mg.

7. The method of any one of claims 1 to 5, wherein the daily dosage is about 1.8 mg.

8. The method of any one of claims 1 to 7 wherein the peptide is administered subcutaneously.

9. The method of any one of claims 1 to 8 wherein the peptide is SEQ ID NO: 6.

10. The method of any one of claims 1-9, further comprising administering a second therapeutic agent.

11. The method of claim 10, wherein the second therapeutic agent is an anti-diabetic agent.

12. The method of claim 10, wherein the second therapeutic agent is an anti-obesity agent.

13. A single unit dose comprising a dosage of about 0.75 mg to about 2.5 mg of a peptide comprising the amino acid sequence of SEQ ID NO: 2.

14. The single unit dose of claim 13, comprising comprising a dosage of about 0.75 mg to about 2.5 mg of a peptide comprising the amino acid sequence of SEQ ID NO: 6.

15. The single unit dose of claim 13 or 14, comprising a dosage of about 1.0 mg to about 2.0 mg of the peptide.

16. The single unit dose of claim 13 or 14, comprising a dosage of about 1.8 mg of the peptide.

17. A kit, device, or container comprising the single unit dose of any one of claims 13-16.

[0125] It is understood that all description of therapeutic methods, pharmaceutical compositions, kits and other similar embodiments described herein contemplate that reference to the peptides include all pharmaceutically acceptable salts, esters, conjugates or prodrugs thereof. Specific embodiments of the invention are further described in the following, nonlimiting examples which illustrate various features. The examples should not be construed as limiting the scope of the invention, as many variations of these embodiments may be practiced and are understood in view of the entire disclosure herein.

EXAMPLES

EXAMPLE 1

[0082] This examples provides a method of making a peptide of SEQ ID NO: 2.

[0083] MBHA resin (4-methylbenzhydrylamine polystyrene resin was used during peptide synthesis. MBHA resin, 100-180 mesh, 1% DVB cross-linked polystyrene; loading of 0.7-1.0 mmol/g), Boc-protected and Fmoc protected amino acids were purchased from Midwest Biotech. The solid phase peptide syntheses using Boc-protected amino acids were performed on an

Applied Biosystem 430A Peptide Synthesizer. Fmoc protected amino acid synthesis was performed using the Applied Biosystems Model 433 Peptide Synthesizer.

[0084] *Peptide synthesis (Boc amino acids/ HF cleavage):*

[0085] Synthesis of the peptide was performed on the Applied Biosystem Model 430A Peptide Synthesizer. Synthetic peptides were constructed by sequential addition of amino acids to a cartridge containing 2 mmol of Boc protected amino acid. Specifically, the synthesis was carried out using Boc DEPBT-activated single couplings. At the end of the coupling step, the peptidyl-resin was treated with TFA to remove the N-terminal Boc protecting group. It was washed repeatedly with dimethylformamide (DMF) and this repetitive cycle was repeated for the desired number of coupling steps. After the assembly, the sidechain protection, Fmoc, was removed by 20% piperidine treatment and acylation was conducted using DIC. The peptidyl-resin at the end of the entire synthesis was dried by using dichloromethane (DCM), and the peptide was cleaved from the resin with anhydrous HF.

[0086] After removal of the protecting groups and before HF cleavage, cyclization was performed as described previously (see, e.g., International Patent Application Publication No. WO2008/101017).

[0087] *HF treatment of the peptidyl-resin*

[0088] The peptidyl-resin was treated with anhydrous hydrogen fluoride (HF), and this typically yielded approximately 350 mg (~50% yield) of a crude deprotected-peptide. Specifically, the peptidyl-resin (30 mg to 200 mg) was placed in the HF reaction vessel for cleavage. 500 μ L of p-cresol was added to the vessel as a carbonium ion scavenger. The vessel was attached to the HF system and submerged in the methanol/dry ice mixture. The vessel was evacuated with a vacuum pump and 10 ml of HF was distilled to the reaction vessel. This reaction mixture of the peptidyl-resin and the HF was stirred for one hour at 0° C, after which a vacuum was established and the HF was quickly evacuated (10-15 min). The vessel was removed carefully and filled with approximately 35 ml of ether to precipitate the peptide and to extract the p-cresol and small molecule organic protecting groups resulting from HF treatment. This mixture was filtered utilizing a teflon filter and repeated twice to remove all excess cresol. This filtrate was discarded. The precipitated peptide dissolves in approximately 20 ml of 10% acetic acid (aq). This filtrate, which contained the desired peptide, was collected and lyophilized.

[0089] An analytical HPLC analysis of the crude solubilized peptide was conducted under the following conditions [4.6 X 30 mm Xterra C8, 1.50 mL/min, 220 nm, A buffer 0.1% trifluoroacetic acid (TFA)/10% acrylonitrile (CAN), B buffer 0.1% TFA/100% ACN, gradient 5-95%B over 15 minutes]. The extract was diluted twofold with water and loaded onto a 2.2 X 25 cm Vydac C4 preparative reverse phase column and eluted using an acetonitrile gradient on a Waters HPLC system (A buffer of 0.1% TFA/10% ACN, B buffer of 0.1% TFA/10% ACN and a gradient of 0-100% B over 120 minutes at a flow of 15.00 ml/min. HPLC analysis of the purified peptide demonstrated greater than 95% purity and electrospray ionization mass spectral analysis was used to confirm the identity of the peptide.

[0090] *Peptide Acylation*

[0091] Acylated peptides were prepared as follows. Peptides were synthesized on a solid support resin using either a CS Bio 4886 Peptide Synthesizer or Applied Biosystems 430A Peptide Synthesizer. In situ neutralization chemistry was used as described by Schnolzer et al., Int. J. Peptide Protein Res. 40: 180-193 (1992). For acylated peptides, the target amino acid residue to be acylated was substituted with an N ϵ -Fmoc lysine residue. Treatment of the completed N-terminally BOC protected peptide with 20% piperidine in DMF for 30 minutes removed Fmoc/formyl groups. Coupling to a free ϵ -amino Lys residue can be achieved by coupling a ten-fold molar excess of either an Fmoc-protected spacer amino acid (ex. Fmoc-Glu-OtBu) or acyl chain (ex. CH₃(CH₂)₁₄-COOH) and PyBOP or DEPBT coupling reagent in DMF/*N,N*-diisopropylethylamine (DIEA). Subsequent removal of the spacer amino acid's Fmoc group is followed by repetition of coupling with an acyl chain. Final treatment with 100% TFA resulted in removal of any side chain protecting groups and the N-terminal BOC group. Peptide resins were neutralized with 5% DIEA/DMF, dried, and then cleaved from the support using HF/*p*-cresol, 95:5, at 0°C for one hour. Following ether extraction, a 5% acetic acid (HOAc) solution was used to solvate the crude peptide. A sample of the solution was then verified to contain the correct molecular weight peptide by ESI-MS. Correct peptides were purified by RP-HPLC using a linear gradient of 10% acetonitrile (CH₃CN)/0.1% TFA to 0.1% TFA in 100% CH₃CN. A Vydac C18 22 mm x 250 mm protein column was used for the purification. Acylated peptide analogs generally completed elution by a buffer ratio of 20:80. Portions were pooled together and checked for purity on an analytical RP-HPLC. Pure fractions were lyophilized yielding white, solid peptides.

[0092] *Analysis using mass spectrometry*

[0093] The mass spectra were obtained using a Sciex API-III electrospray quadrupole mass spectrometer with a standard ESI ion source. Ionization conditions that were used are as follows: ESI in the positive-ion mode; ion spray voltage, 3.9 kV; orifice potential, 60 V. The nebulizing and curtain gas used was nitrogen flow rate of .9 L/min. Mass spectra were recorded from 600-1800 Thompsons at 0.5 Th per step and 2 msec dwell time. The sample (about 1mg/mL) was dissolved in 50% aqueous acetonitrile with 1% acetic acid and introduced by an external syringe pump at the rate of 5 µL/min.

[0094] When the peptides were analyzed in PBS solution by ESI MS, they were first desalted using a ZipTip solid phase extraction tip containing 0.6 µL C4 resin, according to instructions provided by the manufacturer (Millipore Corporation, Billerica, MA, see the Millipore website of the world wide web at millipore.com/catalogue.nsf/docs/C5737).

[0095] *High Performance Liquid Chromatography (HPLC) analysis:*

[0096] Preliminary analyses were performed with these crude peptides to get an approximation of their relative conversion rates in Phosphate Buffered Saline (PBS) buffer (pH, 7.2) using high performance liquid chromatography (HPLC) and MALDI analysis. The crude peptide samples were dissolved in the PBS buffer at a concentration of 1 mg/ml. 1 ml of the resulting solution was stored in a 1.5 ml HPLC vial which was then sealed and incubated at 37 °C. Aliquots of 100µl were drawn out at various time intervals, cooled to room temperature and analyzed by HPLC.

[0097] The HPLC analyses were performed using a Beckman System Gold Chromatography system using a UV detector at 214 nm. HPLC analyses were performed on a 150 mm x 4.6 mm C18 Vydac column. The flow rate was 1 ml/min. Solvent A contained 0.1% TFA in distilled water, and solvent B contained 0.1% TFA in 90% CH₃CN. A linear gradient was employed (40% to 70%B in 15 minutes). The data were collected and analyzed using Peak Simple Chromatography software.

EXAMPLE 2

[0098] A randomized, double-blind, placebo-controlled, multiple ascending dose study was performed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of a peptide of SEQ ID NO: 6 in adult patients with Type 2 diabetes, over 14 days of treatment. The

patients were given doses of 0.25 mg, 0.75 mg, 1.5 mg, 2.0 mg, or 2.5 mg of peptide, or placebo, administered once daily by subcutaneous injection.

[0099] Patients included in the study had been diagnosed with Type 2 diabetes according to WHO criteria at least 3 months prior to screening, were on a stable dose of metformin for at least 2 months prior to screening, and exhibited evidence of insulin secretory capacity (e.g., fasting serum C-peptide levels above 1.5 ng/mL). In addition, fasting plasma glucose prior to the study during was ≤ 240 mg/dL and hemoglobin A1c (HbA1C) level was $\geq 6.5\%$ and $\leq 10.5\%$. Patients were randomized in a 3:1 ratio to receive either active drug or placebo as daily subcutaneous injection into the abdomen for 14 days.

[00100] *Therapeutic effect*

[00101] Based on the data generated from this study, the therapeutic dose range for effects on glucose control in Type 2 diabetic patients ranged from 0.75 mg to 2.5 mg. This dose range is based on efficacy assessments showing that 0.25 mg had effects that were no different from effects seen with placebo. In contrast, the doses ranging from 0.75 mg to 2.5 mg had meaningful decreases in both fasting plasma glucose and meal tolerance tests, as well as in HbA1c, after 14 days of treatment. All of these parameters indicate improved glycemic control and utility in treating diabetes. Hence, this data supports the use of peptide comprising SEQ ID NO: 6 in the treatment of diabetes by administering daily doses ranging from 0.75 mg to 2.5 mg.

[00102] *Fasting plasma glucose*

[00103] Fasting plasma glucose was monitored for the patients receiving the peptide of SEQ ID NO: 6. During a 14 day study, fasting plasma glucose is the best measure of efficacy. The mean change from baseline (i.e. predose on Day 1) in fasting plasma glucose over time and by dose group is depicted in FIGURE 1.

[00104] The effect of the 0.25 mg dose of peptide was no different from placebo. Fasting plasma glucose was slightly reduced by 20 mg/dL in both groups, most likely as a consequence of hospitalization and standardized diet. With the higher doses, there was a clear dose dependent reduction of fasting plasma glucose, with the maximum effect on fasting plasma glucose attained after 11 to 14 days of treatment. All of the doses from 0.75 through 2.5 mg produced meaningful decreases compared to placebo (as well as compared to the 0.25 mg dose). Doses of 0.75 mg,

1.5 mg, 2.0 mg and 2.5 mg achieved a fasting plasma glucose reduction of approximately 39, 36, 42 and 65 mg/dL, respectively.

[00105] *Meal tolerance test*

[00106] A meal tolerance test, which assesses stimulated glucose responses, was also conducted for the patients receiving the peptide of SEQ ID NO: 6. Results of meal tolerance tests are shown in FIGURES 2A-2D for baseline, Day 1, Day 7 and Day 14.

[00107] The effect of the 0.25 mg dose of peptide was no different from placebo, after 14 days. In contrast, for the 0.75 mg dose and higher doses, there was a positive and dose-dependent decrease of postprandial plasma glucose concentration following the meal tolerance test. C_{\max} and AUC_{0-4h} of glucose were clearly reduced with higher doses. After 2 weeks of treatment with 0.75, 1.5, 2.0 or 2.5 mg of peptide, the postprandial glucose C_{\max} was reduced by 20.6, 30.0, 24.8 and 38.1% relative to baseline, respectively, compared to a 5.3 or 8.4% reduction seen for placebo or 0.25 mg, respectively. Similar reductions from baseline were observed for glucose AUC_{0-4h} : 25.4, 33.6, 32.1 and 40.1% reduction was observed for doses of 0.75, 1.5, 2.0 and 2.5 mg, respectively, compared to a reduction of 10.4 or 10.5% seen for placebo or 0.25 mg, respectively.

[00108] *HbA1c*

[00109] Other parameters such as HbA1c, which acts as an integrated measure of daily glucose levels, require longer periods of treatment, usually between 6-12 weeks, to see meaningful and consistent effects.

[00110] A small HbA1c reduction (-0.23%) was seen with placebo, probably due to hospitalization and standardized diet. As observed for the fasting plasma glucose and meal tolerance test above, the effect at 0.25 mg (-0.09%) was no different from placebo. Higher doses produced an approximately 2-fold greater reduction in HbA1c compared to placebo. HbA1c was reduced by 0.41, 0.50, 0.13 and 0.67% (absolute value) after 2 weeks of treatment with 0.75, 1.5, 2.0 and 2.5 mg, respectively. The small sample size and the less advanced disease of patients in the 2.0 mg dose group may explain the relatively minor HbA1c decrease (-0.13%) seen in that group.

[00111] *Pharmacokinetics*

[00112] The pharmacokinetics of the peptide of SEQ ID NO: 6 were non-linear, with greater accumulation at steady state than predicted from single dose data. While the steady state exposures (C_{max} and AUC) increased proportionally with doses from 0.25 to 0.75 mg, steady state exposure increased in a greater than dose-proportional manner between 0.75 and 1.5 mg, with mean C_{max} and mean AUC increasing by approximately 5.1 and 5.8-fold, respectively, compared to the actual dose increase of only 2-fold. At higher doses, the steady state exposures increased again proportionally with doses between 1.5 and 2.5 mg.

[00113] The AUC and C_{max} pharmacokinetic parameters also demonstrate that the ineffective dose of 0.25 mg is well distinguished from the effective dose of 0.75 mg. The AUC for the 0.75 mg dose was 65.1 ng*h/mL (CV: 28.1%) at Day 1, and 124 ng*h/mL (CV: 37.8%) at Day 14, compared to AUC for the 0.25 mg dose of 22.4 ng*h/mL (CV: 27.3%) at Day 1 and 35.5 ng*h/mL (CV: 23.3%) at Day 14. The C_{max} for the 0.75 mg dose was 5.59 ng/mL (CV: 40.5%) at Day 1 and 8.46 ng/mL (CV: 35.0%) at Day 14, while C_{max} for the 0.25 mg dose was 1.93 ng/mL (CV: 36.9%) at Day 1 and 2.59 ng/mL (CV: 32.2%) at Day 14.

[00114] *Tolerability*

[00115] No serious adverse events were experienced at any of the doses tested. The reports of side effects showed a tendency towards an increased rate of adverse events with increasing doses. Based on the tolerability profile of the drug, the dose of 2.5 mg is the highest desirable therapeutic dose to be administered. At this dose, 57% of patients had nausea and/or diarrhea, 49% had headache, 43% had abdominal distension and 29% had constipation. Although most of these events were mild to moderate in severity, it is clear that doses higher than this would produce an adverse event profile that would not be acceptable for patients.

[00116] Literature data in a study of 90 Type 2 diabetic patients has shown that treatment with currently marketed GLP-1 analogues or DPP-IV inhibitors has been associated with increased levels of serum lipase and/or amylase, with serum lipase levels increased more than serum amylase levels. For the peptide of SEQ ID NO: 6, abnormal treatment-emergent increases in lipase levels and amylase levels increased in a dose dependent manner. The largest increase of lipase levels was observed at the 2.5 mg dose (Table 1 below).

[00117] Table 1 Summary of Treatment Emergent Lipase and Amylase Elevation

	Placebo (n=13)	0.25 mg (n=8)	0.75 mg (n=9)	1.5 mg (n=9)	2 mg (n=4)	2.5 mg (n=7)
Number of patient(s) with treatment emergent elevation of lipase						
Any > ULN	1	–	2	4	3	6
> ULN and ≤ 3-fold the ULN	1	–	2	3	2	6
>3- and < 6.5-fold the ULN	–	–	–	1	1	–
Number of patient(s) with treatment emergent elevation of amylase						
> ULN and < 1.5-fold the ULN	–	–	2	1	2	–
Number of patient(s) with treatment emergent elevation of both lipase and amylase						
Any > ULN	–	–	1	1	2	–

Lipase ULN=59 IU/L; Amylase ULN=124 IU/L

[00118] Although these increases were considered mild and are known findings with currently marketed GLP-1 analogues, the 2.5 mg dose would be considered the maximum dose that could be used.

[00119] All of the above data suggest that the range of doses for the peptide of SEQ ID NO: 6 that can be used in the treatment of patients with type 2 diabetes is from 0.75 mg to 2.5 mg once daily.

EXAMPLE 3

[00120] The human dose range of from 0.75 mg to 2.5 mg once daily was surprisingly about 10-fold higher than the doses that would have been predicted from animal studies disclosed in Int'l Patent Pub. No. WO/2010/011439.

[00121] The peptides of SEQ ID NOS: 5, 6, 7, which include varying lengths of fatty acyl chains, are all encompassed within SEQ ID NO: 2. In a first study, SEQ ID NOS: 5, 6, 7, liraglutide or a vehicle control were injected QD into mice at a dose of 25 or 125 nmol/kg for 7 days. The blood glucose levels of the mice were measured 0 and 7 days after injection with peptide or vehicle control and are shown in FIGURE 3. The effects of SEQ ID NOS: 5, 6 and 7 on blood glucose levels were dramatic. At 25 nmol/kg, these peptides caused about a 50% decrease in blood glucose levels.

[00122] In a second study, SEQ ID NO: 6 was tested at different doses in diet-induced obese (DIO) mice (N=8 per group; average initial body weight = 48 g). Mice were subcutaneously injected QD for one week with vehicle only, liraglutide (at 30 nmol/kg of body weight) or mt-

261 (at 0.3, 1, 3, 10 or 30 nmol/kg of body weight). Blood glucose levels of the mice were measured 0 and 7 days after the first injection and are shown in FIGURE 4.

[00123] Doses as low as 3 nmol/kg of SEQ ID NO: 6 caused a significant decrease in blood glucose levels. The decrease in blood glucose levels of mice injected with 3 nmol/kg SEQ ID NO: 6 was similar to the decrease of blood glucose levels of mice injected with 30 nmol/kg liraglutide, demonstrating the higher potency of SEQ ID NO: 6 as compared to liraglutide.

[00124] Liraglutide is an acylated peptide that is a GLP-1 agonist, like the peptide of SEQ ID NO: 2, that is not significantly different in molecular weight from SEQ ID NO: 2. Based on the rodent data in WO/2010/011439, it would have been predicted that the effective dose of SEQ ID NO: 2 in humans should be about 10-fold less than the effective dose of liraglutide. However, the data from human clinical studies described herein demonstrate that a surprisingly higher dose of peptides of SEQ ID NO: 2 is necessary to achieve a meaningful therapeutic effect compared to placebo.

[00125] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[00126] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted.

[00127] Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range and each endpoint, unless otherwise indicated herein, and each separate value and endpoint is incorporated into the specification as if it were individually recited herein.

[00128] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate

the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[00129] Preferred embodiments of this invention are described herein. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

WHAT IS CLAIMED:

1. A peptide for use in improving glycemic control in an adult human, said comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, wherein the use is characterized by a once daily dosage of about 0.75 mg to about 2.5 mg.
2. The peptide of claim 1, wherein the adult human has type 2 diabetes, optionally non-insulin dependent or insulin dependent.
3. The peptide of claim 1, wherein the adult human is a type 2 diabetic patient being treated with a stable dose of metformin.
4. A peptide for use in reducing weight gain or inducing weight loss in an adult human, said peptide comprising the amino acid sequence of any of SEQ ID NOs: 2-8, or a pharmaceutically acceptable salt thereof, wherein the use is characterized by a once daily dosage of about 0.75 mg to about 2.5 mg.
5. The peptide of claim 4 for use in treating obesity.
6. The peptide of any one of claims 1 to 5, wherein the daily dosage is about 1.0 mg to about 2.0 mg.
7. The peptide of any one of claims 1 to 5, wherein the daily dosage is about 1.8 mg.
8. The peptide of any one of claims 1 to 7, wherein the peptide is for administering subcutaneously.
9. The peptide of any one of claims 1 to 8, wherein the peptide is SEQ ID NO: 6.
10. The peptide of any one of claims 1-9, for use in conjunction with a second therapeutic agent.

11. The peptide of claim 10, wherein the second therapeutic agent is an anti-diabetic agent.
12. The peptide of claim 10, wherein the second therapeutic agent is an anti-obesity agent.
13. A single unit dose of a peptide comprising the amino acid sequence of SEQ ID NO: 2 in an amount consisting of about 0.75 mg to about 2.5 mg.
14. The single unit dose of claim 13, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 6.
15. The single unit dose of claim 13 or 14, comprising the peptide in an amount consisting of about 1.0 mg to about 2.0 mg.
16. The single unit dose of claim 13 or 14, comprising the peptide in an amount consisting of about 1.8 mg.
17. A kit, device, or container comprising the single unit dose of any one of claims 13-16.

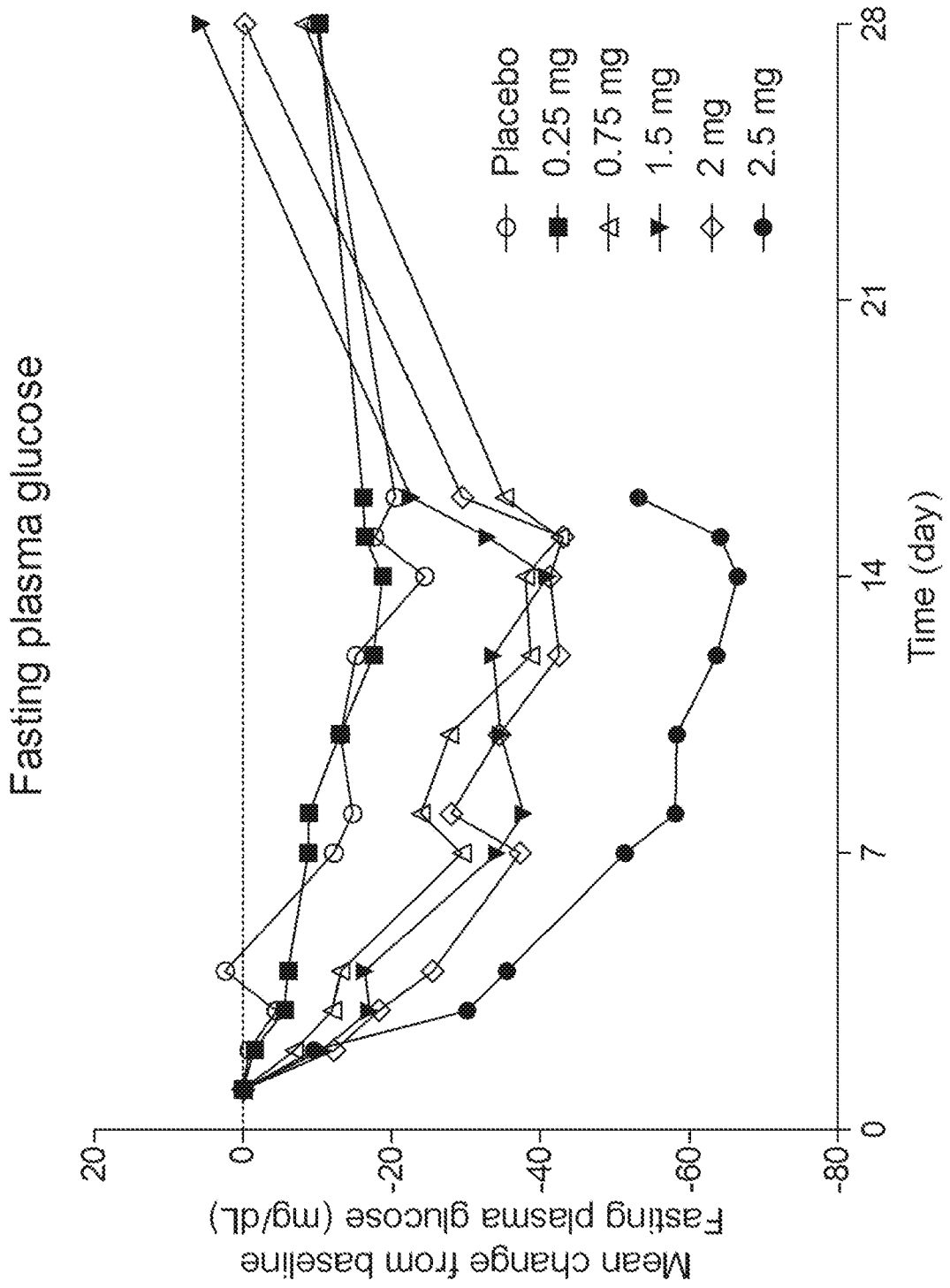


FIGURE 1

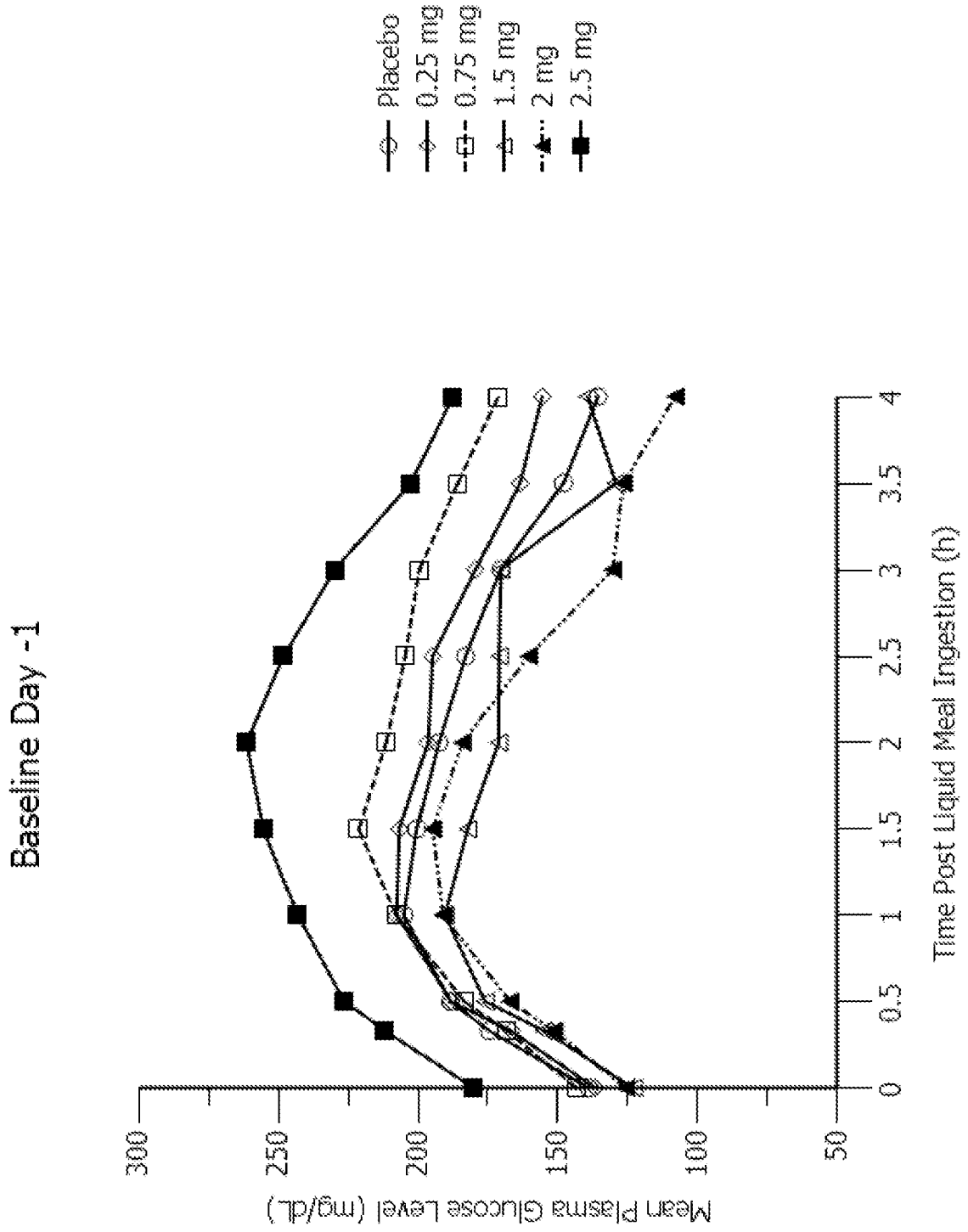


FIGURE 2A

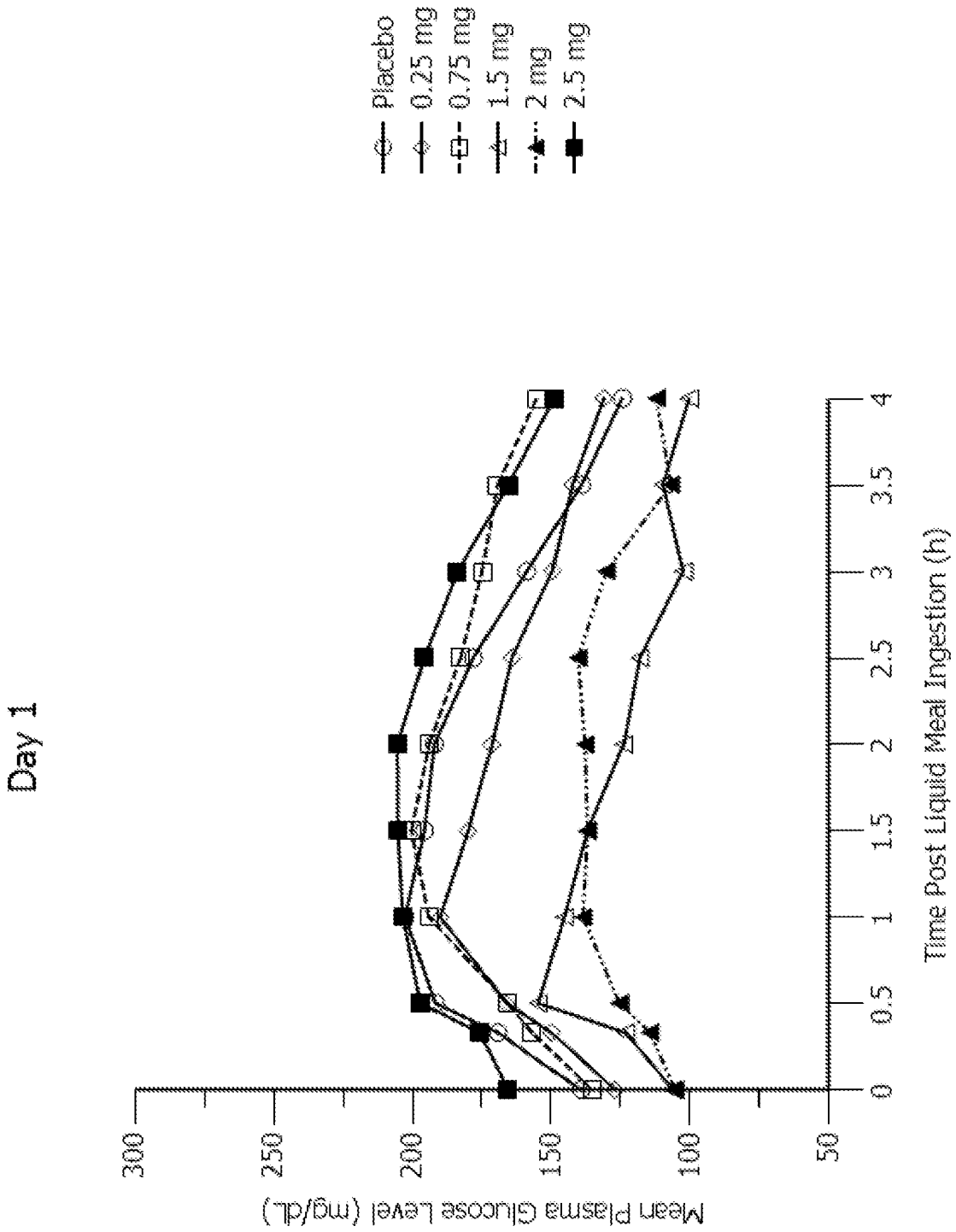


FIGURE 2B

Day 7

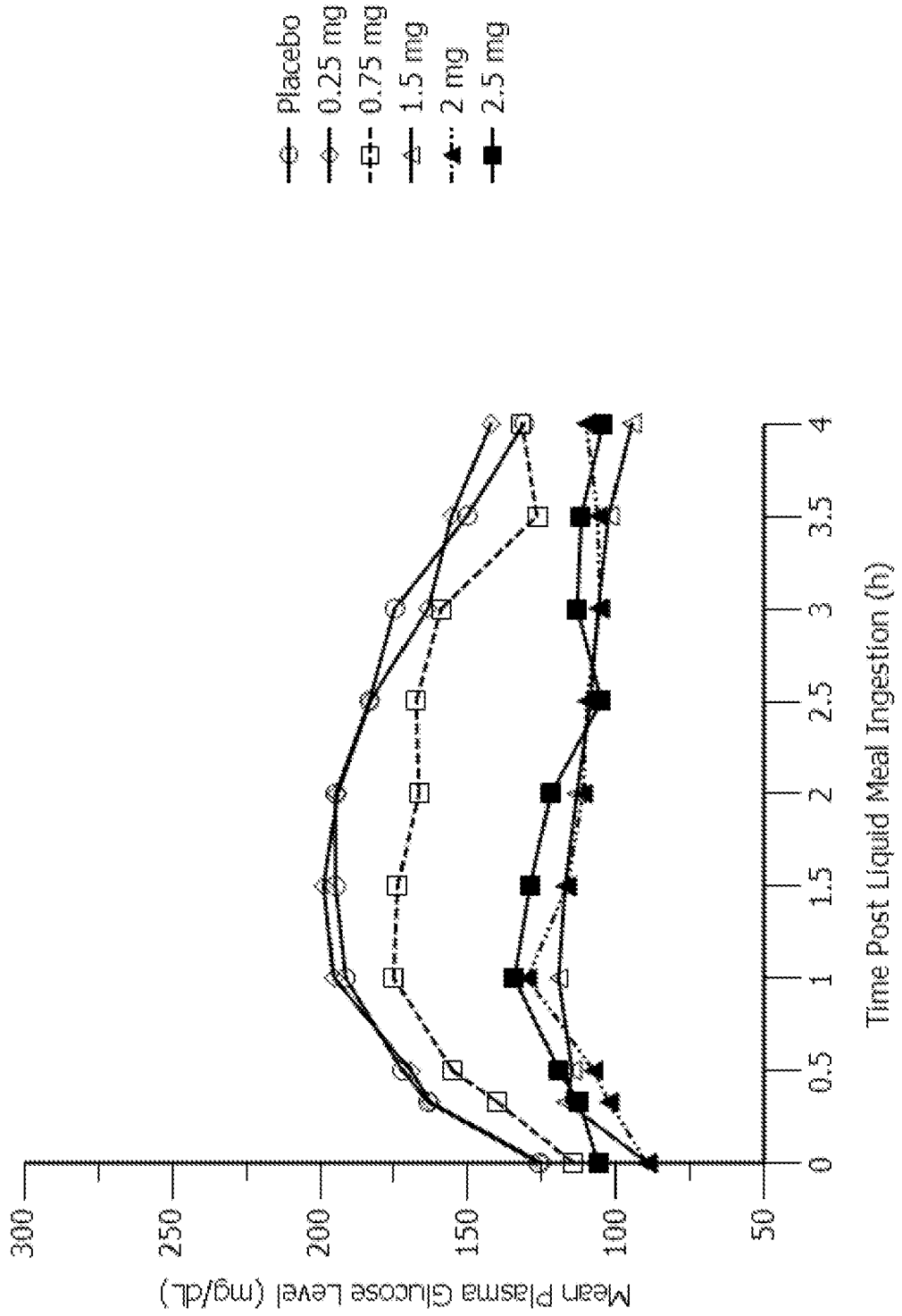


FIGURE 2C

5/7

Day 14

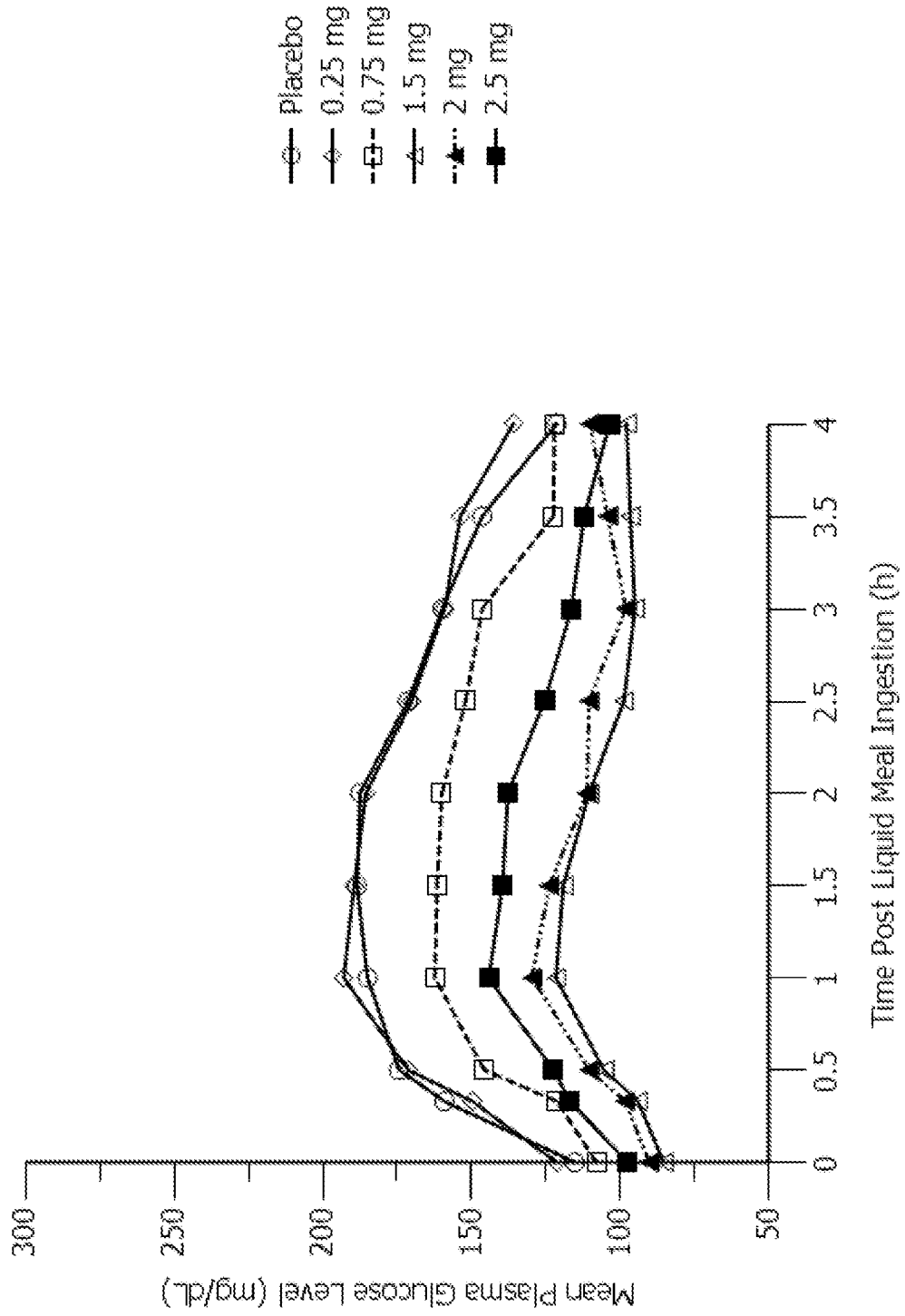


FIGURE 2D

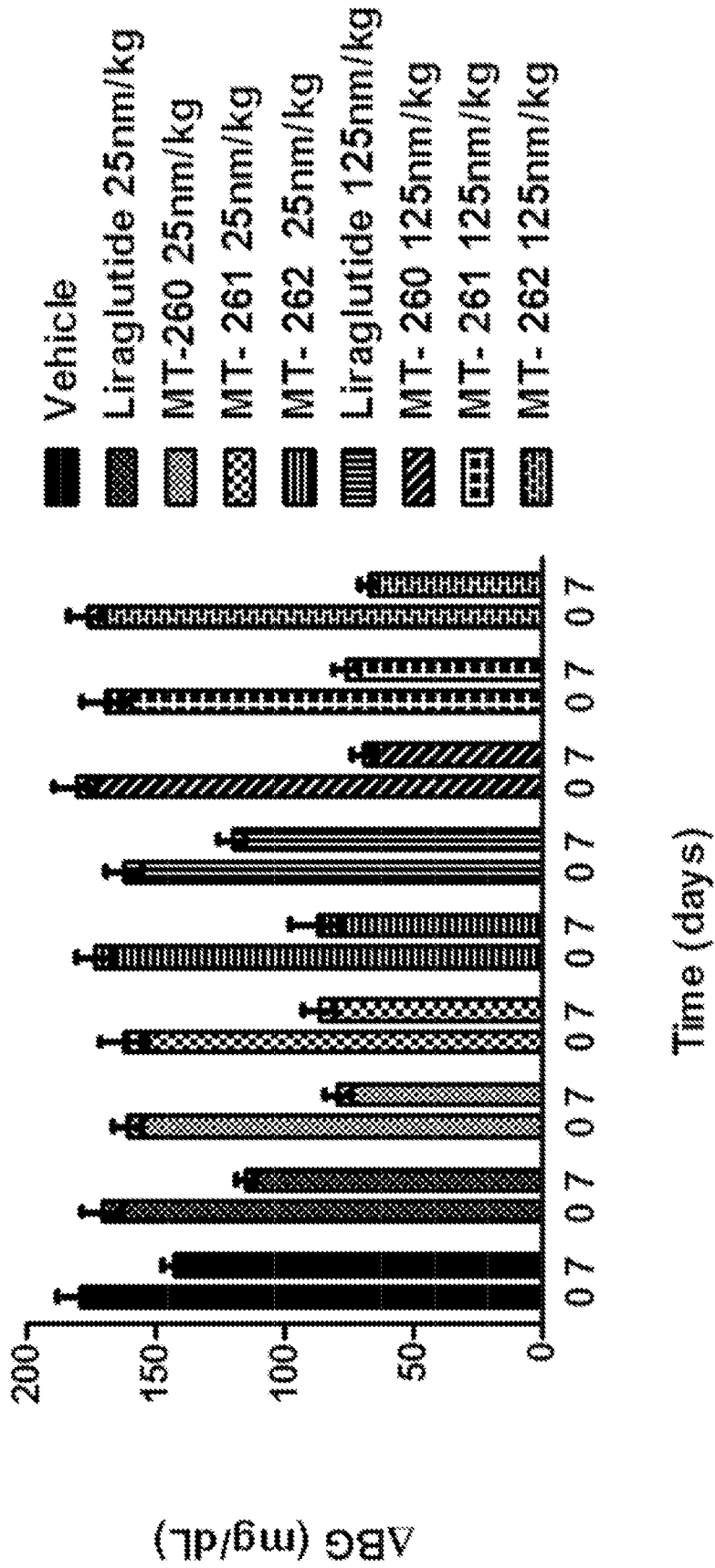


FIGURE 3

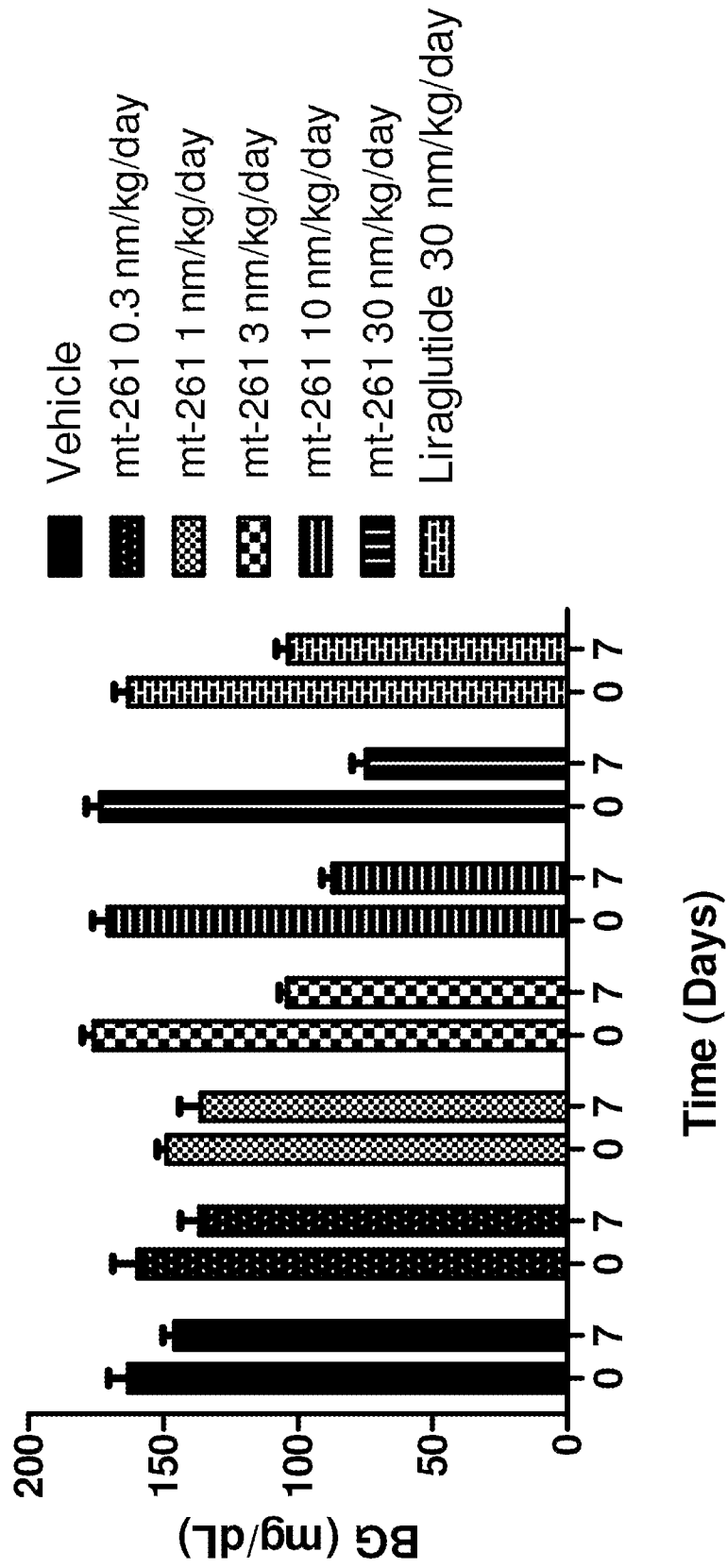


FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/054857

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/26 A61P3/04 A61P3/10
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/088116 A2 (UNIV INDIANA RES & TECH CORP [US]; DIMARCHI RICHARD D [US]; WARD BRIAN) 28 June 2012 (2012-06-28)	1-17
Y	abstract; claims sequences 10, 134, 138 paragraph [00465] sequences 10,134,138	1-17
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Y	abstract sequences 104, 105, 106, 111, 147, 235, 276, 286, 410 claims	1-17
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 25 November 2014	Date of mailing of the international search report 03/12/2014
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Camilleri, Alain
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/054857

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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