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(54) **Title:** METHODS OF TREATING SEVERE NON-DIABETIC OBESITY

(57) **Abstract:** Disclosed herein are methods of treating severe non-diabetic obesity with an oxyntomodulin derivative conjugate administered once weekly at a dose of about 5 mg to about 10 mg. The oxyntomodulin derivative conjugate comprises an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

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METHODS OF TREATING SEVERE NON-DIABETIC OBESITY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/640,463, filed March 8, 2018, the disclosure of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The instant disclosure is directed to methods of treating severe non-diabetic obesity.

BACKGROUND

[0003] The prevalence of obesity is increasing worldwide. The World Health Organization (WHO) estimated that worldwide obesity has nearly tripled since 1975, affecting more than 650 million adults. In the U.S. in 2015-2016, 39.8% of adults and 18.5% of children and adolescents were obese, representing a significantly increasing trend compared to the prevalence of 30.5% and 13.9%, respectively, reported in the 1999-2000 period. The U.S. Centers for Disease Control and Prevention predict that obesity-related deaths could soon overtake smoking-related illnesses as the leading cause of mortality in the U.S. Indeed, obesity represents a major risk factor for cardiovascular (CV) diseases, metabolic diseases, conditions of the genito-urinary system, and musculoskeletal apparatus. In addition, obesity is associated with impaired quality of life, an increased risk of depression, and several types of cancers, predominantly of the digestive tract and female reproductive system. The increased obesity-related morbidity was recently demonstrated in the Patient Outcome Research to Advance Learning study of more than 12 million individuals in the U.S. who were overweight or had obesity and assessed for the prevalence of cardiometabolic risk factors: elevated blood pressure, elevated triglycerides, low high-density lipoprotein-cholesterol (HDL-C), and prediabetes. (JMIR Res Protoc. 2016 Jun 15;5(2)). Compared with being overweight, obesity classes I (body mass index (BMI) 30.0-34.9 kg/m^2), II (BMI 35.0-39.9 kg/m^2), and III (BMI $\geq$40 kg/m^2) were associated with a nearly 2-fold, 3-fold, and 4-fold, respectively, greater probability of having at least 1 cardiometabolic risk factor. Hence, subjects with severe obesity (BMI $\geq$ 35 kg/m^2) are consequently more affected by the disease, have a poor quality of life, and thus have the greatest

need for weight-loss therapy. Indeed, these comorbid conditions are expected to improve or go into remission in the presence of effective and sustained weight loss.

[0004] Current treatments for severe obesity include dietary and behavioral interventions, pharmacologic therapies, and eventually bariatric surgery. While combination strategies using diet, exercise, and behavior therapy have been shown to be more effective in the short term than diet and exercise alone, these treatments are usually ineffective in subjects who are severely obese. Additionally, weight regain is common in severely obese patients, even when approaches are used that combine dietary therapy with exercise and behavior modification.

[0005] Pharmacotherapy is the second-line therapy recommended when lifestyle changes are ineffective in yielding significant weight loss. These pharmacological compounds, however, have variable efficacy and their use is limited by a number of side effects.

SUMMARY

[0006] Provided herein are methods of treating severe non-diabetic obesity in a subject, the method comprising administering about 5 mg to about 10 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an immunoglobulin G4 (IgG4) Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0007] The use of an oxyntomodulin derivative conjugate in the preparation of a medicament for treating severe non-diabetic obesity in a subject is also disclosed, wherein the oxyntomodulin derivative conjugate comprises: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region. The medicament contains about 5 mg, about 7.4 mg, or about 10 mg of the oxyntomodulin derivative conjugate.

[0008] Disclosed is the use of a unit dose containing about 5 mg, about 7.4 mg, or about 10 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 5 mg, about 7.4 mg, or about 10 mg of the oxyntomodulin derivative conjugate, respectively, in a single day in a method of

treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0009] Also provided is an oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject, wherein the oxyntomodulin derivative conjugate comprises: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region, and wherein:

the method comprises administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 5 mg;

the method comprises administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 7.4 mg; or

the method comprises administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 10 mg.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0010] The disclosed methods and uses may be understood more readily by reference to the following detailed description. It is to be understood that the disclosed methods and uses are not limited to the specific methods and uses described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the disclosed methods and uses.

[0011] Unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the disclosed methods and uses are not to be constrained by the correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement.

[0012] Throughout this text, the descriptions refer to methods and uses. Where the disclosure describes a feature or embodiment associated with a method, such a feature or embodiment is equally applicable to the uses. Likewise, where the disclosure describes a feature

or embodiment associated with a use, such a feature or embodiment is equally applicable to the methods.

[0013] Where a range of numerical values is recited or established herein, the range includes the endpoints thereof and all the individual integers and fractions within the range, and also includes each of the narrower ranges therein formed by all the various possible combinations of those endpoints and internal integers and fractions to form subgroups of the larger group of values within the stated range to the same extent as if each of those narrower ranges was explicitly recited. Where a range of numerical values is stated herein as being greater than a stated value, the range is nevertheless finite and is bounded on its upper end by a value that is operable within the context of the invention as described herein. Where a range of numerical values is stated herein as being less than a stated value, the range is nevertheless bounded on its lower end by a non-zero value. It is not intended that the scope of the invention be limited to the specific values recited when defining a range. All ranges are inclusive and combinable.

[0014] When values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. Reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise.

[0015] It is to be appreciated that certain features of the disclosed methods and uses which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed methods and uses that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

[0016] As used herein, the singular forms "a," "an," and "the" include the plural.

[0017] Various terms relating to aspects of the description are used throughout the specification and embodiments. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0018] The term "about" when used in reference to numerical ranges, cutoffs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. Thus, the term "about" is used to encompass variations of ± 10% or less,

variations of ± 5% or less, variations of ± 1% or less, variations of ± 0.5% or less, or variations of ± 0.1% or less from the specified value.

[0019] The term "baseline" refers to the level/amount of the endpoint of interest (bodyweight, BMI, fasting lipids, etc.) in the subject prior to administering the oxyntomodulin derivative conjugate to the subject.

[0020] The term "comprising" is intended to include examples encompassed by the terms "consisting essentially of" and "consisting of"; similarly, the term "consisting essentially of" is intended to include examples encompassed by the term "consisting of."

[0021] Severe non-diabetic obesity is defined as a body mass index (BMI) $\geq$ 35 kg/m^2 to $\leq$ 50 kg/m^2, wherein the obesity is not the result of diabetes.

[0022] *The Impact of Weight on Quality of Life-Lite (IWQOL-Lite)* - The IWQOL-Lite (as discussed in Kolotkin 2001 and Kolotkin 2002) is a 31-item, self-report obesity-specific measure that contains 5 domains: Physical Function (11 items), Self-esteem (7 items), Sexual Life (4 items), Public Distress (5 items), and Work (4 items). It has been used to quantitatively assess an individual's perception of how their weight affects their day-to-day life. The IWQOL-Lite has been widely used in clinical trials and is a reliable and valid measure that has demonstrated good psychometric properties. Confirmatory factor analyses provide strong support for the adequacy of the scale structure. The 5 identified scales and the total score demonstrated excellent psychometric properties in obese patients, and the reliability of the scales ranges from 0.90 to 0.94 and is 0.96 for the total score. A published algorithm is used to calculate domain and total scores, which range from 0 to 100 with higher scores indicating better well-being.

[0023] *Single Item Ease of Weight Management* - A single item that inquires "How difficult is it for you to lose weight?"

[0024] *Patient Activation Measure (PAM)* - PAM is a 13-item self-report measure that identifies where individuals place within 4 different levels of activation. It reliably predicts future emergency room visits, hospital admissions and readmissions, and medication adherence.

[0025] *Eating-related Concepts Questionnaire (ERCQ)* - ERCQ describes the subject's rating eating-related concepts such as hunger, appetite, cravings, and satiety.

[0026] *PROMIS Physical Function Short Form 8b* - PROMIS® (Patient-Reported Outcomes Measurement Information System) is a set of person-centered measures that evaluate

physical, mental, and social health in adults and children (as discussed at the HealthMeasures website - http://www.healthmeasures.net/explore-measurement-systems/promis). These measures can be used with the general population and with individuals living with chronic conditions. PROMIS Profile instruments are a collection of short forms containing a fixed number of items from different domains (Depression, Anxiety, Physical Function, Pain Interference, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities).

[0027] *Patient Global Impression Status (PGIS) and Patient Global Impression of Change (PGIC)* - The PGIS and the PGIC will be used as anchor-based methods (linked to an external criterion) to determine meaningful change in scores for the ERCQ and the PROMIS SF 8b in the population of non-diabetic severely obese subjects. The PGIS contains questions on how the subject would currently rate their ability on the concept(s) of interest. The PGIC contains questions on how the subject would rate their ability on the concept(s) of interest compared to before starting the study.

[0028] The following abbreviations are used herein: oxyntomodulin (OXM); body mass index (BMI); fasting plasma glucose (FPG); Homeostasis Model Assessment for B cell function (HOMA-B); Homeostasis Model Assessment of Insulin Resistance (HOMA-IR); systolic blood pressure (SBP); diastolic blood pressure (DBP); patient-reported outcomes (PROs); hemoglobin A1c (HbA1c); low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); very low-density lipoprotein cholesterol (VLDL-C); glucagon-like peptide-1 receptor (GLP1R); glucagon receptor (GCGR); and subcutaneous (SC).

[0029] Due to the variable efficacy and side effects associated with current pharmacotherapy for severe non-diabetic obesity, there is a need for more effective and well-tolerated weight-management therapies. The disclosed methods and uses address this need.

[0030] Provided herein are methods of treating severe non-diabetic obesity in a subject, the method comprising administering about 5 mg to about 10 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity. The oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an immunoglobulin G4 (IgG4) Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0031] Native oxyntomodulin (OXM; SEQ ID NO: 1) is an endogenous 37-amino acid peptide secreted from enteroendocrine L-cells in the gut in response to, and in proportion to, nutrient ingestion. Oxyntomodulin is a dual agonist, acting at both the glucagon-like peptide-1 receptor (GLP-1R) and the glucagon receptor (GCGR). The disclosed oxyntomodulin derivative conjugate (known as JNJ-64565111; formerly HM12525A; also referred to as "study drug") comprises a synthetic, modified OXM peptide comprising the amino acid sequence of SEQ ID NO: 2 (provided in Table 1) that is covalently conjugated to a constant region of the human immunoglobulin G4 fragment (IgG4 Fc region) via a polyethylene glycol (PEG) linker. The oxyntomodulin derivative portion of the conjugate is a GLP-1/glucagon dual agonist peptide, which, *in vitro*, stimulates both GLP-1R and GCGR with comparable potency. The IgG4 Fc region was chosen as the stabilizing agent because it is a highly prevalent blood protein, has an *in vivo* half-life of several weeks, and lacks immune effector functions (such as complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity). The IgG4 Fc region prolongs the half-life of the oxyntomodulin derivative allowing weekly dosing of oxyntomodulin derivative conjugate, which could not be accomplished with the native oxyntomodulin peptide (which has a very short half-life).

[0032] In some embodiments, the polyethylene glycol comprises a 10 kD polyethylene glycol.

Table 1.

Sequence	SEQ ID NO:
HSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRNRNNIA	1 (native OXM)
HAibQGTFTSDYSKYLD**E**KRA**K**EFVQWLMNTC	2 (OXM derivative)

Aib = 2-aminoisobutyric acid (also known as α-aminoisobutyric acid (AIB) or α-methylalanine or 2-methylalanine).

[0033] The oxyntomodulin derivative portion of the conjugate has a lactam ring that is formed by the underlined and bold residues in SEQ ID NO: 2 (Glu (E) at position 16 and Lys (K) at position 20).

[0034] In some embodiments, the method comprises administering about 5 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0035] In some embodiments, the method comprises administering about 7.4 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0036] In some embodiments, the method comprises administering about 10 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0037] The "once weekly" administration of the oxyntomodulin derivative conjugate is performed within a single day. Preferably, the "once weekly" administration of the oxyntomodulin derivative is performed in a single step, such as a single injection.

[0038] The disclosed methods are performed in subjects having severe non-diabetic obesity, with a body mass index (BMI) of ≥ 35 kg/m^2 to ≤ 50 kg/m^2 prior to the administering.

[0039] In some embodiments, the administering comprises a subcutaneous injection. Suitable sites for the subcutaneous injection include the abdominal area, front of the thigh, back or side of the upper arm, lower back, or buttocks.

[0040] After the administering, the subject can exhibit a reduction in body weight. In some embodiments, the subject can exhibit a reduction in body weight of at least 3% relative to

the subject's baseline body weight. In some embodiments, the subject can exhibit a reduction in body weight of at least 5% relative to the subject's baseline body weight. In some embodiments, the subject can exhibit a reduction in body weight of at least 7.5% relative to the subject's baseline body weight. In some embodiments, the subject can exhibit a reduction in body weight of at least 10% relative to the subject's baseline body weight.

[0041] After the administering, the subject can also exhibit an improvement in body mass index (BMI), waist circumference, fasting lipid levels, fasting plasma glucose (FPG) levels, fasting insulin levels, fasting C-peptide levels, Homeostasis Model Assessment for B cell function (HOMA-B), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, pulse-pressure product, patient-reported outcomes (PROs), hemoglobin A1c (HbA1c), or any combination thereof compared to the subject's baseline value. Fasting lipid levels comprise total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides, or a combination thereof.

[0042] Also provided is the use of the disclosed oxyntomodulin derivative conjugate in the preparation of a medicament for treating non-diabetic obesity in a subject. The medicament contains about 5 mg, about 7.4 mg, or about 10 mg of the oxyntomodulin derivative conjugate.

[0043] Some embodiments provide the use of a unit dose containing about 5 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 5 mg of the oxyntomodulin derivative conjugate in a single day in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0044] Some embodiments provide the use of a unit dose containing about 7.4 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 7.4 mg of the oxyntomodulin derivative conjugate in a single day in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between

residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0045] Some embodiments provide the use of a unit dose containing about 10 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 10 mg of the oxyntomodulin derivative conjugate in a single day in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0046] An oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject is also provided, wherein the oxyntomodulin derivative conjugate comprises: an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; an IgG4 Fc region; and a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region, the method comprising:

administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 5 mg;

administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 7.4 mg; or

administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 10 mg.

EXAMPLES

[0047] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

Study Design

[0048] A randomized, double-blind, placebo-controlled and open-label active-controlled, parallel-group, 5-arm, multicenter study will be performed to assess the use of an

oxyntomodulin derivative conjugate in non-diabetic, severely obese subjects who are ≥18 and ≤70 years of age and have a BMI ≥ 35 to ≤ 50 kg/m^2. The oxyntomodulin derivative conjugate, JNJ-64565111, includes an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20; a human IgG4 Fc region; and a polyethylene glycol that covalently links the oxyntomodulin derivative and the IgG4 Fc region.

[0049] On Day 1, study subjects who meet eligibility criteria will be randomly assigned treatment with placebo, JNJ-64565111 (5.0 mg, 7.4 mg, or 10.0 mg) or open-label liraglutide, stratified by ABPM sub-study participation (yes or no), and then will enter a 26-week treatment phase.

[0050] Efficacy evaluations will include the percentage change in body weight from baseline as the primary efficacy endpoint. Safety evaluations will include the monitoring of AEs (including protocol-specified AEs of interest), vital sign measurements, clinical laboratory tests (including calcitonin, lipase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin), urinalysis, review of concomitant medications, and serum pregnancy testing.

[0051] Subjects who withdraw from the study will not be replaced.

[0052] An interim analysis will be performed when approximately 90% of subjects have either completed or discontinued prior to approximately 10 weeks of study drug treatment. The objective of this interim analysis is to identify active treatment groups, if any, associated with safety or tolerability issues and to facilitate planning of the Phase 3 program.

Study Design Rationale

[0053] The study was designed in general accordance with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance on the development of medications and clinical investigations for the treatment of obesity.

Efficacy Measures

[0054] The primary efficacy endpoint will be a comparison of percentage change in body weight between the JNJ-64565111-treated and placebo-treated groups. This is an accepted endpoint for clinical trials of weight-management products (FDA. Guidance for Industry Patient-

Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009). Safety and tolerability will also be evaluated.

[0055] Secondary endpoints will include the proportion of subjects in each treatment group who lose ≥ 5% and ≥ 10% of baseline body weight and the mean absolute change in body weight, both of which are also accepted endpoints in weight-management studies.

[0056] The effects of JNJ-64565111 compared with liraglutide after 26 weeks of treatment on: the absolute change and percentage change in body weight from baseline; the proportion of subjects with ≥ 5% weight loss from baseline; and the proportion of subjects with ≥ 10% weight loss from baseline will also be evaluated.

[0057] Change from baseline in SBP, DBP, pulse rate, pulse-pressure product, and fasting lipid levels (total cholesterol, LDL-C, HDL-C, and triglycerides) will be evaluated to assess the effects of JNJ-64565111 on the common weight-related comorbidities of hypertension and dyslipidemia. Additional exploratory measures of efficacy include the change from baseline in BMI, waist circumference, FPG, fasting insulin, fasting C-peptide, serum β-hydroxybutyrate, Homeostasis Model Assessment for B cell function (HOMA-B) and HOMA-insulin resistance (IR), IWQOL-Lite, single item Generic Rating of Health, single item Ease of Weight Management, Patient Activation Measure (PAM), and in English-speaking subjects in selected countries only, eating-related concept question (ERCQ), the PROMIS physical function short form 8b (PROMIS SF 8b), an Anticipations of Clinical Trial Treatment (ACTT) pre-trial interview, and a modified Safety, Tolerability, and Efficacy Preview (STEP) exit interview will be evaluated to identify additional treatment effects.

Subject Population

[0058] The randomized study population consists of non-diabetic severely obese subjects, ages 18 to 70 years, inclusive, at screening who have a BMI ≥ 35 kg/m^2 to ≤50 kg/m^2. Men and women will be enrolled in this study. In this study the definition of "severe" obesity, which is commonly used within the surgical community to refer to subjects who are eligible for bariatric surgery, is inclusive of the WHO definition of Obese Class II (35-39 kg/m^2) and III (≥40 kg/m^2) (World Health Organization. World Health Factsheet, Fact sheet N°311 Updated October 2017).

Dosage and Administration

Drug Administration

[0059] Injections of JNJ-64565111 (or matching placebo) and liraglutide can be done at any time of day irrespective of meals. However, it is preferable that the general time of day (i.e., morning, evening, just prior to bed, etc.) for injecting study drug be kept consistent, to the extent possible.

Double-blind JNJ-64565111 or Matching Placebo

[0060] Subjects randomly assigned to double-blind JNJ-64565111 (or matching placebo) are to administer study drug SC once-weekly for the entire duration of the 26-week treatment phase or until early discontinuation. Subjects are to inject to the 4 quadrants of the anterior abdominal wall.

[0061] JNJ-64565111 (or matching placebo) is to be taken on the same day of the week throughout the study (i.e., the regularly scheduled study drug day).

Open-label Liraglutide (SAXENDA®)

[0062] Subjects randomly assigned to open-label liraglutide are to administer study drug SC once daily for the entire duration of the 26-week treatment phase or until early drug discontinuation. Subjects may administer liraglutide SC either in the abdomen, thigh, or upper arm. The injection site may be changed at any time.

Data Analysis

[0063] Data and statistical analyses will be performed to determine efficacy of the study drug.

[0064] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

[0065] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

EMBODIMENTS

[0066] The following list of embodiments is intended to complement, rather than displace or supersede, the previous descriptions.

Embodiment 1. A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering about 5 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an immunoglobulin G4 (IgG4) Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

Embodiment 2. A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering about 7.4 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

Embodiment 3. A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering about 10 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

Embodiment 4. The method of any one of embodiments 1-3, wherein the subject has a body mass index (BMI) of ≥ 35 kg/m^2 to ≤ 50 kg/m^2 prior to the administering.

Embodiment 5. The method of any one of the previous embodiments, wherein the administering comprises subcutaneous injection.

Embodiment 6. The method of any one of the previous embodiments, wherein the subject exhibits a reduction in body weight after administration.

Embodiment 7. The method of embodiment 6, wherein the subject exhibits a reduction in body weight of at least 3% relative to the subject's baseline body weight.

Embodiment 8. The method of any one of the previous embodiments, wherein the subject exhibits an improvement in body mass index (BMI), waist circumference, fasting lipid levels, fasting plasma glucose (FPG) levels, fasting insulin levels, fasting C-peptide levels, Homeostasis Model Assessment for B cell function (HOMA-B), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, pulse-pressure product, patient-reported outcomes (PROs), hemoglobin A1c (HbA1c), or any combination thereof after administration compared to the subject's baseline value.

Embodiment 9. The method of embodiment 8, wherein the fasting lipid levels comprise total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides, or a combination thereof.

Embodiment 10. The method of any one of the previous embodiments, wherein the oxyntomodulin derivative conjugate is JNJ-64565111.

Embodiment 11. The use of an oxyntomodulin derivative conjugate in the preparation of a medicament for treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region

wherein the medicament contains about 5 mg, about 7.4 mg, or about 10 mg of the oxyntomodulin derivative conjugate.

Embodiment 12. Use of a unit dose containing about 5 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 5 mg of the oxyntomodulin derivative conjugate in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

Embodiment 13. Use of a unit dose containing about 7.4 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 7.4 mg of the oxyntomodulin derivative conjugate in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

Embodiment 14. Use of a unit dose containing about 10 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 10 mg of the oxyntomodulin derivative conjugate in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

Embodiment 15. An oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region,

the method comprising administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 5 mg.

Embodiment 16. An oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region,

the method comprising administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 7.4 mg.

Embodiment 17. An oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region,

the method comprising administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 10 mg.

Embodiment 18. The use according to any one of embodiments 11-17, wherein the oxyntomodulin derivative conjugate is JNJ-64565111.

What is claimed:

1. A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering about 5 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an immunoglobulin G4 (IgG4) Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

2. A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering about 7.4 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

3. A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering about 10 mg of an oxyntomodulin derivative conjugate once weekly to the subject to thereby treat the severe non-diabetic obesity, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

4. The method of any one of claims 1-3, wherein the subject has a body mass index (BMI) of ≥ 35 kg/m^2 to ≤ 50 kg/m^2 prior to the administering.

5. The method of any one of the previous claims, wherein the administering comprises subcutaneous injection.

6. The method of any one of the previous claims, wherein the subject exhibits a reduction in body weight after administration.

7. The method of claim 6, wherein the subject exhibits a reduction in body weight of at least 3% relative to the subject's baseline body weight.

8. The method of any one of the previous claims, wherein the subject exhibits an improvement in body mass index (BMI), waist circumference, fasting lipid levels, fasting plasma glucose (FPG) levels, fasting insulin levels, fasting C-peptide levels, Homeostasis Model Assessment for B cell function (HOMA-B), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, pulse-pressure product, patient-reported outcomes (PROs), hemoglobin A1c (HbA1c), or any combination thereof after administration compared to the subject's baseline value.

9. The method of claim 8, wherein the fasting lipid levels comprise total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides, or a combination thereof.

10. The method of any one of the previous claims, wherein the oxyntomodulin derivative conjugate is JNJ-64565111.

11. The use of an oxyntomodulin derivative conjugate in the preparation of a medicament for treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region

wherein the medicament contains about 5 mg, about 7.4 mg, or about 10 mg of the oxyntomodulin derivative conjugate.

12. Use of a unit dose containing about 5 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 5 mg of the oxyntomodulin derivative conjugate in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

13. Use of a unit dose containing about 7.4 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 7.4 mg of the oxyntomodulin derivative conjugate in a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

14. Use of a unit dose containing about 10 mg of an oxyntomodulin derivative conjugate in the manufacture of a medicament for weekly administration of up to a maximum weekly dose of about 10 mg of the oxyntomodulin derivative conjugate in

a method of treating severe non-diabetic obesity in a subject, the oxyntomodulin derivative conjugate comprising:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region.

15. An oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region,

the method comprising administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 5 mg.

16. An oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region,

the method comprising administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 7.4 mg.

17. An oxyntomodulin derivative conjugate for use in a method of treating severe non-diabetic obesity in a subject, wherein the oxyntomodulin derivative conjugate comprises:

an oxyntomodulin derivative comprising the amino acid sequence of SEQ ID NO: 2 and having a ring formation between residues 16 and 20;

an IgG4 Fc region; and

a polyethylene glycol, wherein the polyethylene glycol covalently links the oxyntomodulin derivative and the IgG4 Fc region,

the method comprising administering to the subject the oxyntomodulin derivative conjugate once weekly in an amount of about 10 mg.

18. The use according to any one of claims 11-17, wherein the oxyntomodulin derivative conjugate is JNJ-64565111.