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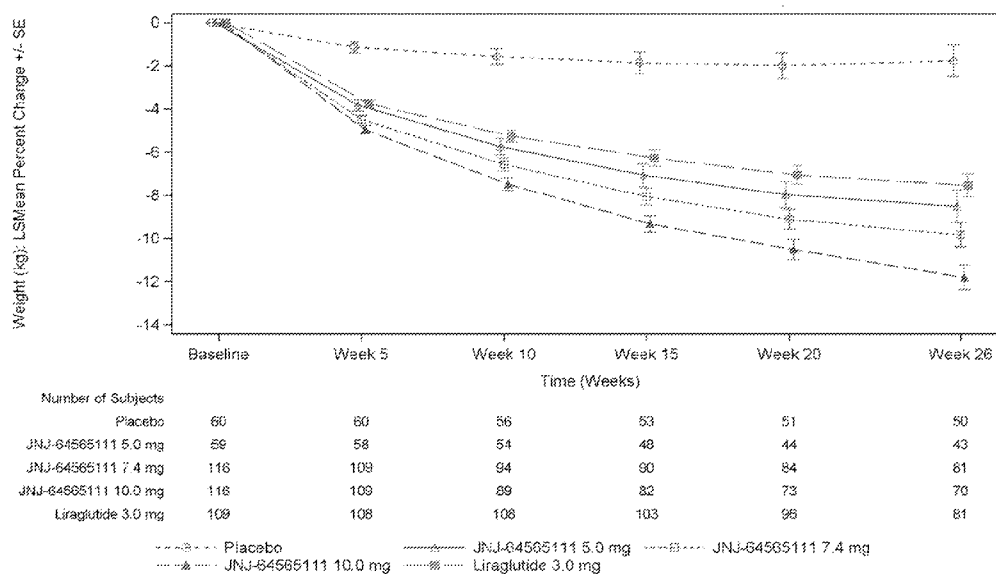


FIG. 1

(57) Abstract: Disclosed herein are methods of treating severe non-diabetic obesity with a fixed dose or multiple ascending dose of an oxyntomodulin derivative conjugate, 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.



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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. 62/782,035, filed December 19, 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<sup>2</sup>), II (BMI 35.0-39.9 kg/m<sup>2</sup>), and III (BMI ≥40 kg/m<sup>2</sup>) 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 ≥35 kg/m<sup>2</sup>) 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 comprising administering a fixed dose of an oxyntomodulin derivative conjugate to the subject. The method comprising administering about 5 mg to about 10 mg of an oxyntomodulin derivative conjugate, once weekly to the 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 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 fixed dose of the oxyntomodulin derivative conjugate as used herein (e.g., about 5 mg to about 10 mg) is the weight of the protein portion of the oxyntomodulin derivative conjugate only (i.e., the oxyntomodulin derivative and IgG4 Fc region without the polyethylene glycol linker).

[0008] 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.

[0009] 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 total 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.

[0010] 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.

[0011] Methods of treating severe non-diabetic obesity in a subject comprising administering multiple ascending doses of an oxyntomodulin derivative conjugate are also provided. The methods comprise:

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate,

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

and wherein the administering is performed according to the following dosing schedule:

- a) an initial dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks;
- b) a second dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks starting two weeks after the initial dose; and
- c) a third dose of the oxyntomodulin derivative conjugate administered once weekly as needed starting four weeks after the initial dose.

**[0012]** The methods of treating severe non-diabetic obesity in a subject comprising administering multiple ascending doses of an oxyntomodulin derivative conjugate can comprise:

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate,

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

and wherein the administering is performed according to the following dosing schedule:

- a) 5 mg of the oxyntomodulin derivative conjugate administered once weekly for two weeks;
- b) 7.4 mg of the oxyntomodulin derivative conjugate administered once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate administered once weekly as needed starting four weeks after the initial dose.

**[0013]** 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:

- a) 5 mg of the oxyntomodulin derivative conjugate once weekly for two weeks;

- b) 7.4 mg of the oxyntomodulin derivative conjugate once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate once weekly as needed starting four weeks after the initial dose

## BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed methods and uses, there are shown in the drawings exemplary embodiments of the methods and uses; however, the methods and uses are not limited to the specific embodiments disclosed. In the drawings:

[0015] **FIG. 1** illustrates the body weight percent changes from baseline over time.

[0016] **FIG. 2** illustrates the proportion of 5% and 10% weight loss responders at week 26. The left bar in each group corresponds to  $\geq 5\%$  weight loss responders; the right bar in each group corresponds to  $\geq 10\%$  weight loss responders.

[0017] **FIG. 3** illustrates an exemplary dosing schedule for the multiple ascending dose study disclosed herein.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0018] The disclosed methods and uses may be understood more readily by reference to the following detailed description taken in connection with the accompanying figure, which forms a part of this disclosure. 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.

[0019] 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.

[0020] 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.

**[0021]** 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.

**[0022]** 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.

**[0023]** 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.

**[0024]** As used herein, the singular forms “a,” “an,” and “the” include the plural.

**[0025]** 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.

**[0026]** 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.

**[0027]** 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.”

[0028] 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  $\pm 10\%$  or less, variations of  $\pm 5\%$  or less, variations of  $\pm 1\%$  or less, variations of  $\pm 0.5\%$  or less, or variations of  $\pm 0.1\%$  or less from the specified value.

[0029] Severe non-diabetic obesity is defined as a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> to  $\leq 50$  kg/m<sup>2</sup>, wherein the obesity is not the result of diabetes.

[0030] As used herein, the fixed dose (for example, 5 mg, 7.4 mg and 10 mg) of the oxyntomodulin derivative conjugate refers to the weight of the protein portion of the oxyntomodulin derivative conjugate only (i.e., the oxyntomodulin derivative and IgG4 Fc region) and therefore excludes the weight of the polyethylene glycol linker. The weight of the protein portion of the oxyntomodulin derivative conjugate can be determined, for example, by measuring an absorbance value of the oxyntomodulin derivative conjugate at a UV wavelength of 280 nm (which measures the absorbance based upon the amino acid content of a protein) and converting the absorbance value to a concentration. An extinction coefficient value of the oxyntomodulin derivative conjugate can be determined as absorbance of the oxyntomodulin derivative conjugate at a unit concentration. This value can be determined as a slope of a line which is plotted using the concentrations against the absorbance values. The weight of the protein portion of the oxyntomodulin derivative conjugate can be determined from the protein concentration.

[0031] *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.

[0032] *Single Item Ease of Weight Management* - A single item that inquires “How difficult is it for you to lose weight?”

[0033] *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.

[0034] *Eating-related Concepts Questionnaire (ERCQ)* - ERCQ describes the subject’s rating eating-related concepts such as hunger, appetite, cravings, and satiety.

[0035] *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).

[0036] *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.

[0037] 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.

Methods of treating severe non-diabetic obesity – fixed dose

[0038] Provided herein are methods of treating severe non-diabetic obesity in a subject comprising administering a fixed dose of an oxyntomodulin derivative conjugate to the subject. The methods can comprise administering about 5 mg to about 10 mg of an oxyntomodulin derivative conjugate once weekly to the subject. 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.

**[0039]** As described above, the fixed dose of the oxyntomodulin derivative conjugate as used herein (e.g., about 5 mg to about 10 mg) is the weight of the protein portion of the oxyntomodulin derivative conjugate only (i.e., the oxyntomodulin derivative and IgG4 Fc region without the polyethylene glycol linker).

**[0040]** 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 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-1 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).

**[0041]** In some embodiments, the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3 (provided in Table 1). In some embodiments, the polyethylene glycol comprises a 10 kD polyethylene glycol. In some embodiments, the oxyntomodulin derivative conjugate is efinopegdutide (also known as JNJ-64565111 and HM12525A; also referred to as “study drug”).

**Table 1. Sequences**

| Sequence | SEQ ID NO: |
|----------|------------|
|----------|------------|

|                                                                                                                                                                                                                                                                                 |                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| HSQGTFTSDYSKYLD <del>SRRA</del> QDFVQWLMNTKRNRNNIA                                                                                                                                                                                                                              | 1<br>(native<br>OXM)     |
| HAibQGTFTSDYSKYLD <u><b>E</b>KRA<u><b>K</b></u></u> EFVQWLMNTC                                                                                                                                                                                                                  | 2<br>(OXM<br>derivative) |
| <u><b>E</b></u> SCPAFEFLG GPSVFLFFPK PKDTLMISRT PEVTCVVVDV SQEDPEVQFN<br>WYVDGVEVHN ARTKPREZQF NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK<br>GLPSSIENTI SKAKGQPREP QVYTLPPSQE EMTENQVSLT CLYKCFYPSD<br>IAVEWESNGQ FENNYKTTTP VLDSOGSEFL YSRLLTVDKSR WQEGNVFSCS<br>VMREALHNNY TQKSLSLSLG K | 3<br>(IgG4 Fc<br>region) |

Aib = 2-aminoisobutyric acid (also known as  $\alpha$ -aminoisobutyric acid (AIB) or  $\alpha$ -methyldalanine or 2-methyldalanine).

[0042] 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).

[0043] In some embodiments, the method comprises administering about 5 mg of an oxyntomodulin derivative conjugate once weekly to the 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.

[0044] In some embodiments, the method comprises administering about 7.4 mg of an oxyntomodulin derivative conjugate once weekly to the 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.

[0045] In some embodiments, the method comprises administering about 10 mg of an oxyntomodulin derivative conjugate once weekly to the 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.

[0046] 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.

[0047] The disclosed methods are performed in subjects having severe non-diabetic obesity, with a body mass index (BMI) of  $\geq 35 \text{ kg/m}^2$  to  $\leq 50 \text{ kg/m}^2$  prior to the administering.

[0048] 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. In some embodiments, the subcutaneous injection is performed in the subject’s upper arm, thigh, abdomen, or a combination thereof. In some embodiments, the subcutaneous injection is performed in the subject’s upper arm or thigh.

[0049] 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.

[0050] 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, LDL-C, HDL-C, VLDL-C, triglycerides, or a combination thereof.

[0051] In some embodiments, the oxyntomodulin derivative conjugate is efinopegdutide.

[0052] 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.

**[0053]** 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 total 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.

**[0054]** 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 total 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.

**[0055]** 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 total 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.

**[0056]** 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.

Methods of treating severe non-diabetic obesity – multiple-ascending dose

**[0057]** Also provided are methods of treating severe non-diabetic obesity comprising administering multiple ascending doses of an oxyntomodulin derivative conjugate to a subject having severe non-diabetic obesity. The methods can comprise:

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate,

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

and wherein the administering is performed according to the following dosing schedule:

- a) an initial dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks;
- b) a second dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks starting two weeks after the initial dose; and
- c) a third dose of the oxyntomodulin derivative conjugate administered once weekly as needed starting four weeks after the initial dose.

**[0058]** The initial dose of the oxyntomodulin derivative conjugate can be about 5 mg or about 7.4 mg. In some embodiments, the initial dose is about 5 mg.

**[0059]** The second dose of the oxyntomodulin conjugate can be about 7.4 mg or about 10 mg. In some embodiments, the second dose is about 7.4 mg.

**[0060]** In some embodiments, the third dose of the oxyntomodulin derivative conjugate is about 10 mg.

**[0061]** In some embodiments, the methods of treating severe non-diabetic obesity in a subject comprise:

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate,

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  
and wherein the administering is performed according to the following dosing schedule:

- a) 5 mg of the oxyntomodulin derivative conjugate administered once weekly for two weeks;
- b) 7.4 mg of the oxyntomodulin derivative conjugate administered once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate administered once weekly as needed starting four weeks after the initial dose.

[0062] Without intending to be bound by theory, the multiple-ascending doses of the oxyntomodulin derivative conjugate will reduce the gastrointestinal adverse events caused by the treatment. Thus, upon treatment with the above dosing schedule, the subject can experience a reduction in gastrointestinal adverse events from the second dose and/or third dose compared to a population of subjects administered an initial dose that is equivalent to the second dose or third dose. For example, when the subject receives an initial dose of 5 mg and a second dose of 7.4 mg, the subject can experience a reduction in gastrointestinal adverse events compared to a population of subjects receiving a fixed dose of 7.4 mg. When the subject receives an initial dose of 5 mg, a second dose of 7.4 mg, and a third dose of 10 mg, the subject can experience a reduction in gastrointestinal adverse events compared to a population of subjects receiving a fixed dose of 7.4 mg or 10 mg. Gastrointestinal adverse events include nausea, vomiting, abdominal distension, dyspepsia, and diarrhea.

[0063] Suitable modes of administering comprises subcutaneous injection. In some embodiments, the subcutaneous injection is performed in the subject's upper arm, thigh, abdomen, or a combination thereof.

[0064] The disclosed methods can be performed on a subject having a body mass index (BMI) of  $\geq 30 \text{ kg/m}^2$  to  $\leq 50 \text{ kg/m}^2$  prior to the administering.

[0065] In some embodiments, the oxyntomodulin derivative conjugate is efinopegdutide.

[0066] Following the administering, the subject can exhibit a reduction in body weight after administration. In some embodiments, the subject can exhibit a reduction in

body weight of at least 3% relative to the subject's baseline body weight. The subject can 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 after administration compared to the subject's baseline value. The fasting lipid levels can comprise total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, or a combination thereof.

[0067] 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:

- a) 5 mg of the oxyntomodulin derivative conjugate once weekly for two weeks;
- b) 7.4 mg of the oxyntomodulin derivative conjugate once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate once weekly as needed starting four weeks after the initial dose

## EXAMPLES

[0068] 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.

### Example 1 – Fixed Dose

#### Study Design

[0069] 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  $\geq 18$  and

≤70 years of age and have a BMI ≥35 to ≤50 kg/m<sup>2</sup>. The oxyntomodulin derivative conjugate, HM12525A (efinopegdutide), 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.

[0070] On Day 1, study subjects who meet eligibility criteria will be randomly assigned treatment with placebo, HM12525A (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.

[0071] 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.

[0072] Subjects who withdraw from the study will not be replaced.

[0073] 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

[0074] 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*

[0075] The primary efficacy endpoint will be a comparison of percentage change in body weight between the HM12525A 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.

[0076] 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.

[0077] The effects of HM12525A 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  $\geq 5\%$  weight loss from baseline; and the proportion of subjects with  $\geq 10\%$  weight loss from baseline will also be evaluated.

[0078] 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 HM12525A 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  $\beta$ -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

[0079] The randomized study population consists of non-diabetic severely obese subjects, ages 18 to 70 years, inclusive, at screening who have a BMI  $\geq 35$  kg/m<sup>2</sup> to  $\leq 50$  kg/m<sup>2</sup>. 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<sup>2</sup>) and III ( $\geq 40$  kg/m<sup>2</sup>) (World Health Organization. World Health Factsheet, Fact sheet N°311 Updated October 2017).

#### Dosage and Administration

##### *Drug Administration*

[0080] Injections of HM12525A (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.

[0081] Double-blind HM12525A or Matching Placebo - Subjects randomly assigned to double-blind HM12525A (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.

[0082] HM12525A (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).

[0083] Open-label Liraglutide (SAXENDA®) - 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*

[0084] Data and statistical analyses will be performed to determine efficacy of the study drug.

#### Clinical Study Results

[0085] All three doses of HM12525A significantly reduced body weight from baseline as compared to placebo. The degree of weight loss was greater with all three doses of HM12525A compared to liraglutide (Table 2 and FIG. 1 and 2).

[0086] Meaningful non-dose dependent mean reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) was observed in all three dose groups compared to placebo and liraglutide (Table 3).

[0087] As shown in Tables 2-11, weekly administration of efinopegdutide at the three doses (5 mg, 7.4 mg, and 10 mg) significantly lowered the body weight and the blood pressure and improved the lipid profile in severe non-diabetic obese subjects.

[0088] As used in Tables 4-11 below, modified intention-to-treat (mITT) refers to the population of subject including those ITT subjects who have taken at least one dose of the study medication and had at least 1 post-baseline body weight measurement. For those subjects randomized to liraglutide, only those who titrated to 3.0 mg were included in the mITT population.

Table 2. Percentage change from baseline in body weight (kg) at week 26

| JNJ-64565111                |                 |                 |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Value at Baseline           | Placebo         | 5 mg            | 7.4 mg          | 10 mg           | Lira 3 mg       |
| N                           | 50              | 58              | 109             | 109             | 108             |
| Mean (SD)                   | 112.74 (17.538) | 112.34 (15.710) | 112.51 (16.933) | 114.63 (15.495) | 114.84 (15.970) |
| % Change from Baseline      |                 |                 |                 |                 |                 |
| LS Mean (SE)                | -1.76 (0.73)    | -8.51 (0.76)    | -9.83 (0.56)    | -11.80 (0.58)   | -7.54 (0.54)    |
| P-value (versus Placebo)(a) |                 | <.001           | <.001           | <.001           | <.001           |
| Diff. of LS Means (SE)      |                 | -6.75 (1.056)   | -8.07 (0.921)   | -10.04 (0.934)  | -5.78 (0.910)   |
| 95% CI (a)                  |                 | {-9.31, -4.19}  | {-10.31, -5.84} | {-12.31, -7.78} | {-7.99, -3.57}  |

Table 3. Change from baseline in vital signs at week 26

| JNJ-64565111          |             |              |              |              |              |
|-----------------------|-------------|--------------|--------------|--------------|--------------|
|                       | Placebo     | 5 mg         | 7.4 mg       | 10 mg        | Lira 3 mg    |
| SBP (mmHg), mean (SD) | 0.0 (10.88) | -6.4 (11.94) | -9.5 (12.41) | -7.6 (10.75) | -0.8 (12.14) |
| DBP (mmHg), mean (SD) | -0.1 (8.05) | -2.7 (7.25)  | -4.0 (9.20)  | -4.1 (6.54)  | 0.4 (8.48)   |



Table 5. Change from baseline in total cholesterol at week 26

| TEFIC03: Change from Baseline in Total Cholesterol at Week 26; Modified Intent-to-Treat (NJI-6456511IOBE2001) |                     |                     |                     |                     |                      |
|---------------------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|---------------------|----------------------|
| NJ-64565111                                                                                                   |                     |                     |                     |                     |                      |
| Analysis set: Modified Intent-To-Treat                                                                        | Placebo             | 5 mg                | 7.4 mg              | 10 mg               | Lara 3 mg            |
| Cholesterol (mg/dL)                                                                                           |                     |                     |                     |                     |                      |
| Value at Baseline                                                                                             |                     |                     |                     |                     |                      |
| N                                                                                                             | 60                  | 59                  | 116                 | 116                 | 109                  |
| Mean (SD)                                                                                                     | 53<br>198.6 (38.75) | 48<br>191.6 (37.85) | 89<br>198.2 (38.90) | 81<br>190.5 (37.46) | 102<br>195.6 (31.71) |
| Change from Baseline                                                                                          |                     |                     |                     |                     |                      |
| LS Mean (SE)                                                                                                  | 2.5 (3.75)          | -19.2 (3.98)        | -24.8 (2.95)        | -26.1 (3.10)        | -4.9 (2.87)          |
| P-value (versus Placebo)(a)                                                                                   |                     | <.001               | <.001               | <.001               |                      |
| Diff. of LS Means (SE)                                                                                        |                     | -21.7 (5.47)        | -27.3 (4.76)        | -28.6 (4.87)        |                      |
| 95% CI (a)                                                                                                    |                     | (-32.4, -10.9)      | (-36.7, -18.0)      | (-38.2, -19.0)      |                      |

<sup>a</sup> Pairwise comparison. CIs are based a mixed model for repeated measures including the fixed effects of treatment, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect.

Note: The table includes subjects who had both baseline and post-baseline measurements.

Note: Nominal p-values are presented.

Table 6. Mean and LS mean change from baseline in LDL-cholesterol over time

| TEFLDLC02: Mean and LS Mean Change From Baseline in LDL-C (conventional units) Over Time; Modified Intent-to-Treat (JNJ-64565111OBE2001) |  |  |                      |    |   |                      |      |    |                      |          |      |
|------------------------------------------------------------------------------------------------------------------------------------------|--|--|----------------------|----|---|----------------------|------|----|----------------------|----------|------|
| Placebo                                                                                                                                  |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  | Change from Baseline |    |   | Change from Baseline |      |    | Change from Baseline |          |      |
|                                                                                                                                          |  |  | LS                   |    |   | LS                   |      |    | LS                   |          |      |
|                                                                                                                                          |  |  | Mean                 | SE | N | Mean(SD)             | Mean | SE | N                    | Mean(SD) | Mean |
| Analysis set: Modified Intent-to-Treat                                                                                                   |  |  |                      |    |   |                      |      |    |                      |          |      |
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|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |
|                                                                                                                                          |  |  |                      |    |   |                      |      |    |                      |          |      |

Table 7. Change from baseline in LDL-cholesterol at week 26

| TEFLIDC03: Change from Baseline in LDL-C (conventional units) at Week 26; Modified Intent-to-Treat (INJ-6456511IOBE3001)                                                                                                                               |  |               |               |               |               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|---------------|---------------|---------------|---------------|
|                                                                                                                                                                                                                                                        |  | INJ-64565111  |               |               |               |
|                                                                                                                                                                                                                                                        |  | Placebo       | 5 mg          | 7.4 mg        | 10 mg         |
| Analysis set: Modified Intent-To-Treat                                                                                                                                                                                                                 |  | 60            | 59            | 116           | 116           |
| LDL Cholesterol (mg/dL)                                                                                                                                                                                                                                |  |               |               |               |               |
| Value at Baseline                                                                                                                                                                                                                                      |  |               |               |               |               |
| N                                                                                                                                                                                                                                                      |  | 53            | 48            | 89            | 81            |
| Mean (SD)                                                                                                                                                                                                                                              |  | 119.0 (34.19) | 112.0 (31.89) | 116.2 (30.15) | 113.0 (32.98) |
| Change from Baseline                                                                                                                                                                                                                                   |  |               |               |               |               |
| LS Mean (SE)                                                                                                                                                                                                                                           |  | 5.1 (3.44)    | -5.4 (3.65)   | -5.3 (2.70)   | -6.8 (2.84)   |
| p-value (versus Placebo)(a)                                                                                                                                                                                                                            |  |               | 0.037         | 0.017         | 0.008         |
| Diff. of LS Means (SE)                                                                                                                                                                                                                                 |  |               | -10.5 (5.02)  | -10.5 (4.38)  | -12.0 (4.47)  |
| 95% CI (a)                                                                                                                                                                                                                                             |  |               | (-20.4, -0.7) | (-19.1, -1.9) | (-20.8, -3.2) |
| <sup>a</sup> Pairwise comparison: CIs are based a mixed model for repeated measures including the fixed effects of treatment, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect. |  |               |               |               |               |
| Note: The table includes subjects who had both baseline and post-baseline measurements.                                                                                                                                                                |  |               |               |               |               |
| Note: Nominal p-values are presented                                                                                                                                                                                                                   |  |               |               |               |               |

Table 8. Mean and LS mean change from baseline in HDL-cholesterol over time

| TEFHDL02: Mean and LS Mean Change From Baseline in HDL-C (conventional units) Over Time; Modified Intent-to-Treat (JNJ-64565111OBE2001) |                                 |              |                      |       |                                   |              |                      |       |                                  |              |                      |       |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--------------|----------------------|-------|-----------------------------------|--------------|----------------------|-------|----------------------------------|--------------|----------------------|-------|
| Analysis set: Modified Intent-to-Treat                                                                                                  | Placebo                         |              |                      |       | JNJ-64565111 5 mg                 |              |                      |       | JNJ-64565111 7.4 mg              |              |                      |       |
|                                                                                                                                         | Change from Baseline LS         |              | Change from Baseline |       | Change from Baseline              |              | Change from Baseline |       | Change from Baseline             |              | Change from Baseline |       |
|                                                                                                                                         | N                               | Mean(SD)     | Mean                 | SE    | N                                 | Mean(SD)     | LS Mean              | SE    | N                                | Mean(SD)     | LS Mean              | SE    |
| HDL Cholesterol (mg/dL)                                                                                                                 |                                 |              |                      |       |                                   |              |                      |       |                                  |              |                      |       |
| Week 15                                                                                                                                 | 53                              | 49.8 (10.58) | -3.39                | 0.851 | 48                                | 43.1 (9.28)  | -11.12               | 0.897 | 89                               | 41.2 (9.54)  | -10.78               | 0.656 |
| Week 26                                                                                                                                 | 49                              | 51.5 (12.15) | -2.11                | 1.000 | 43                                | 46.8 (10.45) | -7.82                | 1.067 | 79                               | 42.7 (10.23) | -9.54                | 0.782 |
| TEFHDL02: Mean and LS Mean Change From Baseline in HDL-C (conventional units) Over Time; Modified Intent-to-Treat (JNJ-64565111OBE2001) |                                 |              |                      |       |                                   |              |                      |       |                                  |              |                      |       |
| Analysis set: Modified Intent-to-Treat                                                                                                  | JNJ-64565111 10 mg              |              |                      |       | Lara 3 mg                         |              |                      |       | Change from Baseline             |              |                      |       |
|                                                                                                                                         | Change from Baseline LS         |              | Change from Baseline |       | Change from Baseline              |              | Change from Baseline |       | Change from Baseline             |              | Change from Baseline |       |
|                                                                                                                                         | N                               | Mean(SD)     | Mean                 | SE    | N                                 | Mean(SD)     | LS Mean              | SE    | N                                | Mean(SD)     | LS Mean              | SE    |
| HDL Cholesterol (mg/dL)                                                                                                                 |                                 |              |                      |       |                                   |              |                      |       |                                  |              |                      |       |
| Week 15                                                                                                                                 | 79                              | 39.8 (8.28)  | -11.62               | 0.695 | 101                               | 46.7 (11.16) | -5.46                | 0.615 |                                  |              |                      |       |
| Week 26                                                                                                                                 | 70                              | 41.2 (7.66)  | -10.04               | 0.828 | 79                                | 50.6 (11.36) | -1.54                | 0.766 |                                  |              |                      |       |
| TEFHDL02: Mean and LS Mean Change From Baseline in HDL-C (conventional units) Over Time; Modified Intent-to-Treat (JNJ-64565111OBE2001) |                                 |              |                      |       |                                   |              |                      |       |                                  |              |                      |       |
| Analysis set: Modified Intent-to-Treat                                                                                                  | JNJ-64565111 5 mg Minus Placebo |              |                      |       | JNJ-64565111 7.4 mg Minus Placebo |              |                      |       | JNJ-64565111 10 mg Minus Placebo |              |                      |       |
|                                                                                                                                         | LS Mean 95% CI                  |              | LS Mean 95% CI       |       | LS Mean 95% CI                    |              | LS Mean 95% CI       |       | LS Mean 95% CI                   |              | LS Mean 95% CI       |       |
|                                                                                                                                         | -7.7 (-10.2; -5.3)              |              | -7.4 (-9.5; -5.3)    |       | -8.2 (-10.4; -6.1)                |              | -7.9 (-10.5; -5.3)   |       | -7.9 (-10.5; -5.3)               |              | -7.9 (-10.5; -5.3)   |       |

<sup>a</sup> Pairwise comparisons. CIs are based on a mixed model for repeated measures including the fixed effects of treatment, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect.

Note: The table includes subjects who had both baseline and post-baseline measurements.

\* Pairwise comparison. CIs are based on a mixed model for repeated measures including the fixed effects of treatment, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect.

Note: The table includes subjects who had both baseline and post-baseline measurements.

Table 9. Change from baseline in HDL-cholesterol at week 26

| TEFHDL03: Change from Baseline in HDL-C (conventional units) at Week 26; Modified Intent-to-Treat (FNI-6456511IOBE2001) |              |              |              |               |              |
|-------------------------------------------------------------------------------------------------------------------------|--------------|--------------|--------------|---------------|--------------|
| FNI-64565111                                                                                                            |              |              |              |               |              |
| Analysis set: Modified Intent-To-Treat                                                                                  | Placebo      | 5 mg         | 7.4 mg       | 10 mg         | 13.3 mg      |
|                                                                                                                         | 60           | 59           | 116          | 116           | 109          |
| HDL Cholesterol (mg/dL)                                                                                                 |              |              |              |               |              |
| Value at Baseline                                                                                                       |              |              |              |               |              |
| N                                                                                                                       | 53           | 48           | 89           | 81            | 102          |
| Mean (SD)                                                                                                               | 53.6 (10.43) | 55.2 (12.45) | 51.8 (12.59) | 50.9 (12.33)  | 51.9 (11.34) |
| Change from Baseline                                                                                                    |              |              |              |               |              |
| LS Mean (SE)                                                                                                            | -2.1 (1.00)  | -7.8 (1.07)  | -9.5 (0.78)  | -10.0 (0.83)  | -1.5 (0.77)  |
| P-value (versus Placebo)(a)                                                                                             |              | <.001        | <.001        | <.001         |              |
| Diff. of LS Means (SE)                                                                                                  |              | -5.7 (1.46)  | -7.4 (1.27)  | -7.9 (1.30)   |              |
| 95% CI (a)                                                                                                              |              | (-8.6, -2.8) | (-9.9, -4.9) | (-10.5, -5.4) |              |

<sup>a</sup> Pairwise comparison: CIs are based a mixed model for repeated measures including the fixed effects of treatment, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect

Note: The table includes subjects who had both baseline and post-baseline measurements.

Note: Nominal p-values are presented

Table 10. Change from baseline in fasting triglycerides at week 15

| IEFTRIG04: Change From Baseline in Fasting Triglycerides (conventional units) at Week 15 (observed); Modified Intent-to-Treat (JNJ-64565110BE2001) |                 |                  |                  |                  |                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------|------------------|------------------|-------------------|
| Analysis set: Modified Intent-To-Treat                                                                                                             | Placebo         | JNJ-64565111     |                  |                  | Lira 3 mg         |
|                                                                                                                                                    |                 | 5 mg             | 7.4 mg           | 10 mg            |                   |
| Triglycerides (mg/dL)                                                                                                                              |                 |                  |                  |                  |                   |
| Value at Baseline                                                                                                                                  |                 |                  |                  |                  |                   |
| N                                                                                                                                                  | 53              | 48               | 89               | 80               | 101               |
| Mean (SD)                                                                                                                                          | 133.4 (83.83)   | 123.1 (49.76)    | 145.3 (84.96)    | 129.1 (49.45)    | 137.6 (72.91)     |
| Median(Min, Max)                                                                                                                                   | 112.0 (35, 560) | 116.5 (50, 244)  | 129.0 (34, 536)  | 128.0 (48, 262)  | 116.0 (50, 499)   |
| Value at Week 15                                                                                                                                   |                 |                  |                  |                  |                   |
| N                                                                                                                                                  | 53              | 48               | 89               | 80               | 101               |
| Mean (SD)                                                                                                                                          | 143.5 (101.39)  | 89.8 (33.35)     | 98.6 (44.05)     | 85.9 (36.97)     | 123.2 (77.97)     |
| Median(Min, Max)                                                                                                                                   | 112.0 (35, 653) | 86.5 (28, 172)   | 88.0 (40, 324)   | 77.0 (33, 246)   | 104.0 (39, 686)   |
| Change from Baseline                                                                                                                               |                 |                  |                  |                  |                   |
| N                                                                                                                                                  | 53              | 48               | 89               | 80               | 101               |
| Mean (SD)                                                                                                                                          | 10.1 (57.33)    | -33.4 (38.50)    | -46.7 (65.87)    | -43.2 (47.12)    | -14.4 (64.24)     |
| Median(Min, Max)                                                                                                                                   | 6.0 (-99, 276)  | -31.5 (-153, 61) | -31.0 (-398, 55) | -40.5 (-182, 83) | -13.0 (-343, 286) |
| P-value (versus Placebo)(a)                                                                                                                        |                 | <.001            | <.001            | <.001            |                   |
| Hodges-Lehman Estimate                                                                                                                             |                 | -35.5            | -40.5            | -45.5            |                   |
| 95% CI (b)                                                                                                                                         |                 | (-51.0, -20.0)   | (-55.0, -26.0)   | (-60.0, -31.0)   |                   |

<sup>a</sup> Note: p-value is based on the Wilcoxon rank sum test.

<sup>b</sup> Distribution-free confidence interval based on the Wilcoxon rank sum test (Hollander and Wolfe, 1999).

Note: The table includes only the subjects who had both baseline and windowed Week 15 triglyceride measurements.

Table 11. Change from baseline in fasting triglycerides at week 26

| IEFIRIG05: Change From Baseline in Fasting Triglycerides (conventional units) at Week 26 (observed); Modified Intent-to-Treat (JNJ-64583111OBE2001) |                 |                  |                  |                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------|------------------|------------------|
| Analysis set: Modified Intent-To-Treat                                                                                                              | Placebo         | JNJ-64583111     |                  |                  |
|                                                                                                                                                     |                 | 5 mg             | 7.4 mg           | 10 mg            |
| Triglycerides (mg/dL)                                                                                                                               |                 |                  |                  |                  |
| Value at Baseline                                                                                                                                   |                 |                  |                  |                  |
| N                                                                                                                                                   | 49              | 43               | 79               | 79               |
| Mean (SD)                                                                                                                                           | 130.2 (84.37)   | 121.1 (50.28)    | 146.8 (87.79)    | 130.7 (58.15)    |
| Median(Min, Max)                                                                                                                                    | 112.0 (35, 560) | 113.0 (50, 244)  | 134.0 (34, 536)  | 129.0 (48, 368)  |
| Value at Week 26                                                                                                                                    |                 |                  |                  |                  |
| N                                                                                                                                                   | 49              | 43               | 79               | 79               |
| Mean (SD)                                                                                                                                           | 123.6 (80.49)   | 95.4 (43.98)     | 97.6 (50.72)     | 84.5 (31.19)     |
| Median(Min, Max)                                                                                                                                    | 105.0 (45, 557) | 89.0 (37, 257)   | 84.0 (27, 305)   | 81.0 (36, 210)   |
| Change from Baseline                                                                                                                                |                 |                  |                  |                  |
| N                                                                                                                                                   | 49              | 43               | 79               | 79               |
| Mean (SD)                                                                                                                                           | -6.6 (37.16)    | -25.7 (47.36)    | -49.2 (78.07)    | -46.2 (54.76)    |
| Median(Min, Max)                                                                                                                                    | -3.0 (-117, 84) | -19.0 (-123, 99) | -37.0 (-421, 89) | -38.5 (-293, 74) |
| P-value (versus Placebo)(a)                                                                                                                         |                 | 0.028            | <.001            | <.001            |
| Hodges-Lehman Estimate                                                                                                                              |                 | -19.5            | -33.0            | -34.5            |
| 95% CI (b)                                                                                                                                          |                 | (-36.0, -3.0)    | (-49.0, -17.0)   | (-50.0, -19.0)   |

<sup>a</sup> Note: p-value is based on the Wilcoxon rank sum test.

<sup>b</sup> Distribution-free confidence interval based on the Wilcoxon rank sum test (Hollander and Wolfe, 1999).

Note: The table includes only the subjects who had both baseline and windowed Week 26 triglyceride measurements.

**Example 2 – Bioavailability By Injection Site**

[0089] This study is designed to examine the relative bioavailability of JNJ-64565111 (efinopegdutide or HM12525A) administered as a subcutaneous (SC) injection at 3 different injection sites: in the upper arm, in the abdomen, and in the thigh of overweight/obese subjects and to assess whether the absorption of JNJ-64565111 differs among these 3 commonly used injection sites.

**Study design**

[0090] The Phase 1 study is a randomized, open-label, single-center, single-dose, 3-period, 6-sequence, crossover study in otherwise healthy overweight/obese male and female subjects. Thirty overweight/obese male and female subjects, aged 18 to 55 years of age, will participate in this study.

[0091] For all subjects enrolled, the study will consist of 3 phases:

1. A screening phase;
2. An open-label treatment phase consisting of 3 single-dose treatment periods of 42 days each (Days 1 to 42); and
3. End-of-study (follow-up) assessments (which take place within 7-14 days after last PK sample collection on Day 42 of Treatment Period 3).

[0092] On Day 1 of Treatment Period 1, subjects will be randomly assigned to 1 of 6 possible treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA) to ensure that they receive all of the following treatments, one in each period:

- Treatment A: 10 mg JNJ-64565111 SC administration in the upper arm in fasted condition;
- Treatment B: 10 mg JNJ-64565111 SC administration in the thigh in fasted condition; and
- Treatment C: 10 mg JNJ-64565111 SC administration in the abdomen in fasted condition.

[0093] The injection will be given in the abdomen, thigh, or upper arm, and the injection site will be interchanged for each dosing visit.

[0094] Each treatment period will have a 6-week PK sampling period and will be separated by a washout period of at least 7 days between the last PK sample collection and dosing on Day 1 of subsequent treatment period.

**Main criteria for inclusion**

[0095] Otherwise healthy overweight/obese men and women between 18 and 55 years of age, inclusive; body mass index between 25-40 kg/m<sup>2</sup>, inclusive, and a body weight of not less than 75 kg.

#### Primary Objective

[0096] The primary objective is to compare the relative bioavailability of JNJ-64565111 10 mg between SC administrations in the upper arm versus the abdomen and between administrations in the thigh versus the abdomen in otherwise healthy overweight/obese subjects.

#### Secondary Objectives

[0097] The secondary objectives are to assess the safety and immunogenicity of JNJ-64565111 in otherwise healthy overweight/obese subjects.

#### Dosage and administration

[0098] JNJ-64565111 is supplied as a solution for SC injection. The drug product (JNJ-64565111) will be supplied as pre-filled syringes (PFSs). Each PFS is filled with a nominal fill volume of 0.5 mL of the same formulation composition at a target protein concentration of 20 mg/mL aqueous solution to deliver 10 mg.

[0099] Following an overnight fast of at least 8 hours, each subject will receive a single dose of JNJ-64565111 in the morning of Day 1 of each treatment period. The treatment of 10 mg JNJ-64565111 will be administered SC. The injection will be given in the abdomen, thigh, or upper arm, the injection site being interchanged for each dosing visit. The abdominal injection site will be located in the right lower quadrant of the abdomen.

#### Pharmacokinetics

[0100] Based on the individual serum concentration-time data, using the actual sampling times, the following PK parameters may be derived for JNJ-64565111 for each injection site: the maximum observed serum analyte concentration ( $C_{max}$ ), the actual sampling time to reach the maximum observed serum analyte concentration ( $t_{max}$ ), the first-order rate constant associated with the terminal portion of the curve ( $\lambda_z$ ), the area under the serum concentration versus time curve from time 0 to time of the last measurable (non-below quantification limit) concentration ( $AUC_{last}$ ), the AUC from time 0 to infinite time ( $AUC_{\infty}$ ), percentage of  $AUC_{\infty}$  obtained by extrapolation ( $\%AUC_{\infty,ex}$ ), the apparent terminal

elimination half-life ( $t_{1/2,\lambda}$ ), the total apparent clearance (CL/F), and the apparent volume of distribution (Vd/F). Other PK parameters may be estimated as appropriate for exploration of the data.

### **Example 3 – Multiple Ascending Dose**

[0101] This study will evaluate whether a titration regimen influences the gastrointestinal tolerability. The proposed titration scheme will start with a dose of 5 mg once weekly for two weeks, followed by 7.4 mg once weekly for the next two weeks and finally 10 mg once weekly for the last two weeks.

#### Study design

[0102] This Phase 1 study is an open-label, multiple-dose, single-center titration study in otherwise healthy obese subjects. Twenty-two otherwise healthy obese male and female subjects, aged 18 to 55 years of age, will participate in this study.

[0103] The titration scheme is exemplified in FIG. 3. Subjects will receive:

- A single SC dose of 5 mg JNJ-64565111 on Days 1 and 8 (with a +1-day dosing window) in fasted condition;
- A single SC dose of 7.4 mg JNJ-64565111 on Days 15 and 22 in fasted condition; and
- A single SC dose of 10 mg JNJ-64565111 on Days 29 and 36 in fasted condition.

#### Main criteria for inclusion

[0104] Otherwise healthy obese men and women between 18 and 55 years of age, inclusive; body mass index between 30-50 kg/m<sup>2</sup>, inclusive, and a body weight of not less than 75 kg.

#### Primary Objective

[0105] The primary objective is to assess the gastrointestinal tolerability of JNJ-64565111 following a dose titration in otherwise healthy obese subjects at 6 weeks.

#### Secondary Objectives

[0106] The secondary objectives are:

- To assess the safety of JNJ-64565111 upon multiple dosing;
- To study the time course of gastrointestinal AEs upon multiple dosing;
- To evaluate the PK of JNJ-64565111; and

- To assess the immunogenicity of JNJ-64565111.

#### Dose and administration

[0107] JNJ-64565111 is supplied as a solution for SC injection. The drug product (JNJ-64565111) will be supplied as PFSs. Each PFS is filled with a nominal fill volume of 0.25, 0.37, or 0.5 mL of the same formulation composition at a target protein concentration of 20 mg/mL aqueous solution to deliver 5 mg, 7.4 mg, or 10 mg, respectively.

[0108] Following an overnight fast of at least 8 hours, JNJ-64565111 will be administered subcutaneously in the abdomen in the morning of Days 1, 8(+1), 15, 22, 29, and 36. All SC injections will be made to the anterior abdominal wall avoiding the 2-inch area around the umbilicus, in the following order:

- Day 1: right lower quadrant
- Day 8(+1): left lower quadrant
- Day 15: left upper quadrant
- Day 22: right upper quadrant
- Day 29: right lower quadrant
- Day 36: left lower quadrant

#### Pharmacokinetics

[0109] The following PK parameters, as a minimum, can be determined where statistically possible for JNJ-64565111:

- After the first dose:  $C_{max}$ ,  $t_{max}$ ,  $AUC_{last}$ , and the area under the serum concentration versus time curve over the dosing interval ( $AUC_{\tau}$ );
- For each subsequent dose:  $C_{max}$  and the observed serum analyte concentration just prior to the beginning or the end of a dosing interval, on Days 8(+1), 15, 22, 29, 36, and 43 ( $C_{trough}$ );
- After the last dose:  $C_{max}$ , the minimum observed serum analyte concentration over the dosing interval ( $C_{min}$ ), the average concentration over the dosing interval  $\tau$  ( $C_{average}$ ),  $t_{max}$ ,  $AUC_{\tau}$ , the observed accumulation index, determined after multiple dose administration ( $AR_{AUC}$ ), and the total apparent clearance of drug after extravascular administration ( $CL/F$ ).

[0110] 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.

[0111] 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

[0112] 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, 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, 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, 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  $\geq 35 \text{ kg/m}^2$  to  $\leq 50 \text{ kg/m}^2$  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 embodiment 5, wherein the subcutaneous injection is performed in the subject's upper arm, thigh, abdomen, or a combination thereof.

**Embodiment 7.** The method of embodiment 6, wherein the subcutaneous injection is performed in the subject's upper arm or thigh.

**Embodiment 8.** The method of any one of the previous embodiments, wherein the subject exhibits a reduction in body weight after administration.

**Embodiment 9.** The method of embodiment 8, wherein the subject exhibits a reduction in body weight of at least 3% relative to the subject's baseline body weight.

**Embodiment 10.** 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 11.** The method of embodiment 10, wherein the fasting lipid levels comprise total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, or a combination thereof.

**Embodiment 12.** The method of any one of the previous embodiments, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

**Embodiment 13.** The method of any one of the previous embodiments, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

**Embodiment 14.** The method of any one of the previous embodiments, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

**Embodiment 15.** 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 16.** 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 total 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 17.** 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 total 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 18.** 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 total 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 19.** The use of any one of embodiments 15-18, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

**Embodiment 20.** The use of any one of embodiments 15-19, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

**Embodiment 21.** The use of any one of embodiments 15-20, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

**Embodiment 22.** 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 23.** 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 24.** 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 25.** The oxyntomodulin derivative conjugate for use of any one of embodiments 22-24, wherein the oxyntomodulin derivative conjugate is subcutaneously administered once weekly in the subject's upper arm, thigh, abdomen, or a combination thereof.

**Embodiment 26.** The oxyntomodulin derivative conjugate for use of embodiment 25, wherein the oxyntomodulin derivative conjugate is subcutaneously administered once weekly in the subject's upper arm or thigh.

**Embodiment 27.** The oxyntomodulin derivative conjugate for use of any one of embodiments 22-26, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

**Embodiment 28.** The oxyntomodulin derivative conjugate for use of any one of embodiments 22-27, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

**Embodiment 29.** The oxyntomodulin derivative conjugate for use of any one of embodiments 22-28, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

**Embodiment 30.** A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate, 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

and wherein the administering is performed according to the following dosing schedule:

- a) an initial dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks;
- b) a second dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks starting two weeks after the initial dose; and
- c) a third dose of the oxyntomodulin derivative conjugate administered once weekly as needed starting four weeks after the initial dose.

**Embodiment 31.** The method of embodiment 30, wherein the initial dose of the oxyntomodulin derivative conjugate is about 5 mg or about 7.4 mg.

**Embodiment 32.** The method of embodiment 30, wherein the second dose of the oxyntomodulin conjugate is about 7.4 mg or about 10 mg.

**Embodiment 33.** The method of embodiment 30, wherein the third dose of the oxyntomodulin derivative conjugate is about 10 mg.

**Embodiment 34.** A method of treating severe non-diabetic obesity in a subject, the method comprising:

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate,

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

and wherein the administering is performed according to the following dosing schedule:

- a) 5 mg of the oxyntomodulin derivative conjugate, administered once weekly for two weeks;
- b) 7.4 mg of the oxyntomodulin derivative conjugate, administered once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate, administered once weekly as needed starting four weeks after the initial dose.

**Embodiment 35.** The method of embodiment 34, wherein the subject experiences a reduction in gastrointestinal adverse events from the second dose and/or third dose compared to a population of subjects administered an initial dose that is equivalent to the second dose or third dose.

**Embodiment 36.** The method of any one of embodiments 30-35, wherein the administering comprises subcutaneous injection.

**Embodiment 37.** The method of embodiment 36, wherein the subcutaneous injection is performed in the subject's upper arm, thigh, abdomen or a combination thereof.

**Embodiment 38.** The method of any one of embodiments 30-37, wherein the subject has a body mass index (BMI) of  $\geq 30 \text{ kg/m}^2$  to  $\leq 50 \text{ kg/m}^2$  prior to the administering.

**Embodiment 39.** The method of any one of embodiments 30-38, wherein the subject exhibits a reduction in body weight after administration.

**Embodiment 40.** The method of embodiment 39, wherein the subject exhibits a reduction in body weight of at least 3% relative to the subject's baseline body weight.

**Embodiment 41.** The method of any one of embodiments 30-40, 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 42.** The method of embodiment 41, wherein the fasting lipid levels comprise total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, or a combination thereof.

**Embodiment 43.** The method of any one of embodiments 30-42, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

**Embodiment 44.** The method of any one of embodiments 30-43, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

**Embodiment 45.** The method of any one of embodiments 30-44, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

**Embodiment 46.** 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:

- a) 5 mg of the oxyntomodulin derivative conjugate, once weekly for two weeks;
- b) 7.4 mg of the oxyntomodulin derivative conjugate, once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate, once weekly as needed starting four weeks after the initial dose.

**Embodiment 47.** The oxyntomodulin derivative conjugate for use of embodiment 46, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

**Embodiment 48.** The oxyntomodulin derivative conjugate for use of embodiment 46 or 47, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

**Embodiment 49.** The oxyntomodulin derivative conjugate for use of any one of embodiments 46-48, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

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, 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, 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, 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  $\geq 35 \text{ kg/m}^2$  to  $\leq 50 \text{ kg/m}^2$  prior to the administering.

5. The method of any one of the previous claims, wherein the administering comprises subcutaneous injection.
6. The method of claim 5, wherein the subcutaneous injection is performed in the subject's upper arm, thigh, abdomen, or a combination thereof.
7. The method of claim 6, wherein the subcutaneous injection is performed in the subject's upper arm or thigh.
8. The method of any one of the previous claims, wherein the subject exhibits a reduction in body weight after administration.
9. The method of claim 8, wherein the subject exhibits a reduction in body weight of at least 3% relative to the subject's baseline body weight.
10. 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.
11. The method of claim 10, wherein the fasting lipid levels comprise total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, or a combination thereof.
12. The method of any one of the previous claims, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.
13. The method of any one of the previous claims, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

14. The method of any one of the previous claims, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

15. 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.

16. 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 total 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.

17. 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 total 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.

18. 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 total 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.

19. The use of any one of claims 15-18, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

20. The use of any one of claims 15-19, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

21. The use of any one of claims 15-20, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

22. 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.

23. 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.

24. 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.

25. The oxyntomodulin derivative conjugate for use of any one of claims 22-24, wherein the oxyntomodulin derivative conjugate is subcutaneously administered once weekly in the subject's upper arm, thigh, abdomen, or a combination thereof.

26. The oxyntomodulin derivative conjugate for use of claim 25, wherein the oxyntomodulin derivative conjugate is subcutaneously administered once weekly in the subject's upper arm or thigh.

27. The oxyntomodulin derivative conjugate for use of any one of claims 22-26, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

28. The oxyntomodulin derivative conjugate for use of any one of claims 22-27, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

29. The oxyntomodulin derivative conjugate for use of any one of claims 22-28, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

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

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate, 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

and wherein the administering is performed according to the following dosing schedule:

- a) an initial dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks;
- b) a second dose of the oxyntomodulin derivative conjugate administered once weekly for two weeks starting two weeks after the initial dose; and
- c) a third dose of the oxyntomodulin derivative conjugate administered once weekly as needed starting four weeks after the initial dose.

31. The method of claim 30, wherein the initial dose of the oxyntomodulin derivative conjugate is about 5 mg or about 7.4 mg.

32. The method of claim 30, wherein the second dose of the oxyntomodulin conjugate is about 7.4 mg or about 10 mg.

33. The method of claim 30, wherein the third dose of the oxyntomodulin derivative conjugate is about 10 mg.

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

administering to the subject a first dose and one or more subsequent doses of an oxyntomodulin derivative conjugate,

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

and wherein the administering is performed according to the following dosing schedule:

- a) 5 mg of the oxyntomodulin derivative conjugate, administered once weekly for two weeks;
- b) 7.4 mg of the oxyntomodulin derivative conjugate, administered once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate, administered once weekly as needed starting four weeks after the initial dose.

35. The method of claim 34, wherein the subject experiences a reduction in gastrointestinal adverse events from the second dose and/or third dose compared to a population of subjects administered an initial dose that is equivalent to the second dose or third dose.

36. The method of any one of claims 30-35, wherein the administering comprises subcutaneous injection.

37. The method of claim 36, wherein the subcutaneous injection is performed in the subject's upper arm, thigh, abdomen or a combination thereof.

38. The method of any one of claims 30-37, wherein the subject has a body mass index (BMI) of  $\geq 30 \text{ kg/m}^2$  to  $\leq 50 \text{ kg/m}^2$  prior to the administering.

39. The method of any one of claims 30-38, wherein the subject exhibits a reduction in body weight after administration.

40. The method of claim 39, wherein the subject exhibits a reduction in body weight of at least 3% relative to the subject's baseline body weight.

41. The method of any one of claims 30-40, 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.

42. The method of claim 41, wherein the fasting lipid levels comprise total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, or a combination thereof.

43. The method of any one of claims 30-42, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

44. The method of any one of claims 30-43, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

45. The method of any one of claims 30-44, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

46. 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:

- a) 5 mg of the oxyntomodulin derivative conjugate, once weekly for two weeks;
- b) 7.4 mg of the oxyntomodulin derivative conjugate, once weekly for two weeks starting two weeks after the initial dose; and
- c) 10 mg of the oxyntomodulin derivative conjugate, once weekly as needed starting four weeks after the initial dose.

47. The oxyntomodulin derivative conjugate for use of claim 46, wherein the IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 3.

48. The oxyntomodulin derivative conjugate for use of claim 46 or 47, wherein the polyethylene glycol comprises a 10 kD polyethylene glycol.

49. The oxyntomodulin derivative conjugate for use of any one of claims 46-48, wherein the oxyntomodulin derivative conjugate is efinopegdutide.

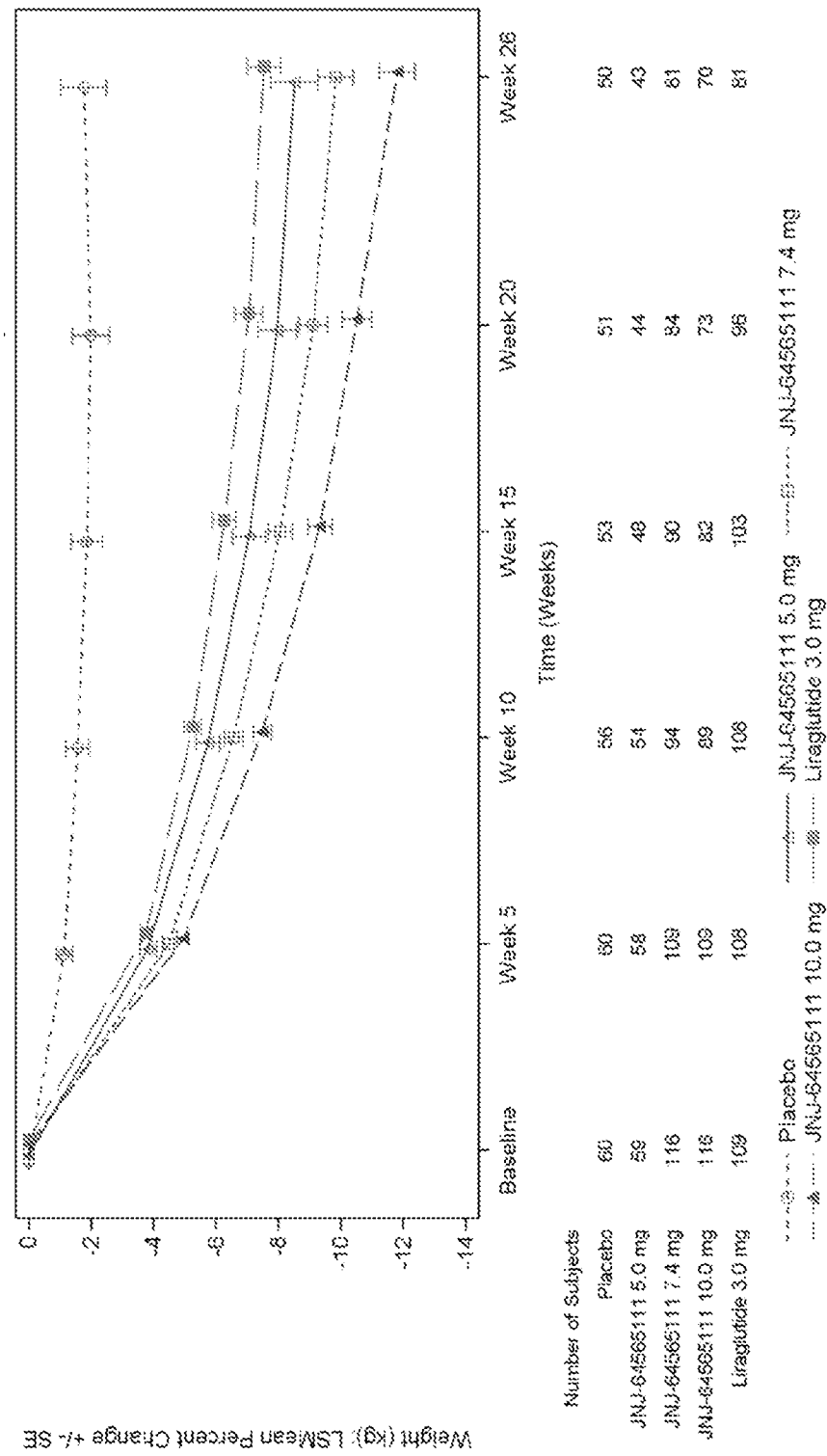


FIG. 1

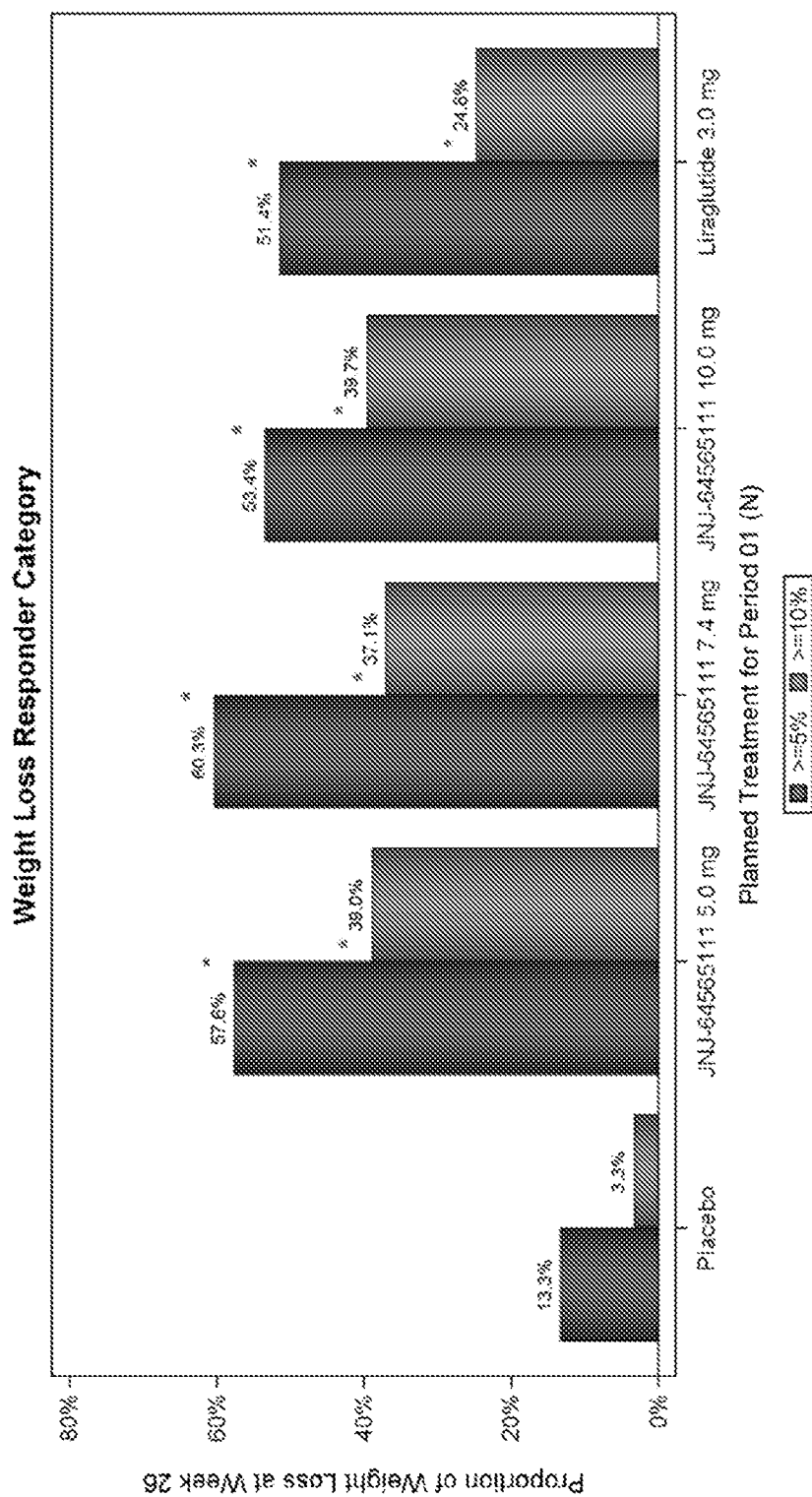


FIG. 2

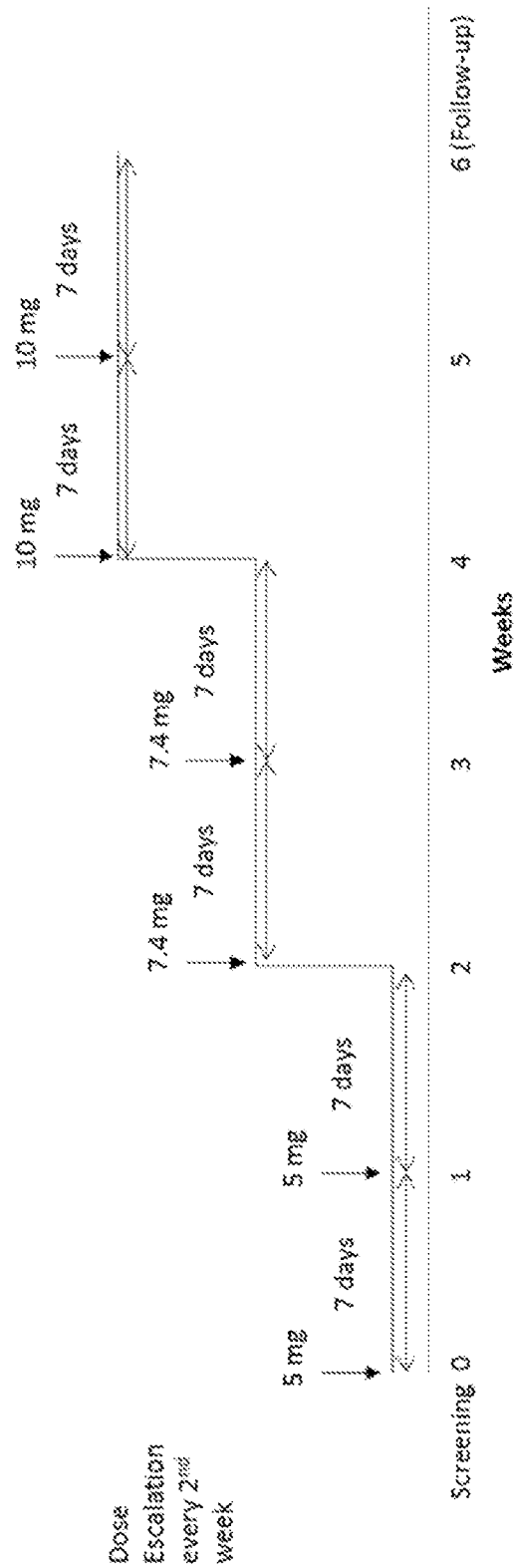


FIG. 3