

METHODS FOR TREATING OBESITY WITH AN MC4R AGONIST

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 63/388,580, filed July 12, 2022; and U.S. Application No. 63/426,610, filed November 18, 2022; the entire contents of each of the foregoing applications are incorporated herein by reference.

BACKGROUND

There is a need for treatment of obesity and obesity-related disorders, including non-genetic obesity and related disorders (e.g., hypothalamic obesity).

SUMMARY OF THE INVENTION

The present disclosure features, *inter alia*, treatments for obesity, e.g., a non-genetic obesity, e.g., hypothalamic obesity, with a compound (e.g., an MC4R agonist) or composition thereof. In some embodiments, the MC4R agonist is a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), (e.g., as described herein) or a pharmaceutically acceptable salt thereof. The MC4R agonist, e.g., a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a pharmaceutically acceptable salt thereof, may be provided as a composition (e.g., a pharmaceutical composition) with a pharmaceutically acceptable excipient. In an embodiment, the pharmaceutically acceptable excipient comprises a polyethylene glycol (e.g., a modified polyethylene glycol) or a lipid (e.g., a neutral lipid or a phospholipid). In an embodiment, the pharmaceutically acceptable excipient comprises a modified polyethylene glycol. In an embodiment, the pharmaceutically acceptable excipient comprises a lipid, such as a neutral diacyl lipid or a phospholipid.

The MC4R agonist or composition thereof may be provided in a unit dosage form. For example, the unit dosage form may comprise between about 0.01 mg to 100 mg of the MC4R agonist. In an embodiment, the unit dosage form comprises between 0.1 mg and 100 mg, e.g., between 0.1 mg and 50 mg, 0.1 mg and 25 mg, 0.1 mg and 10 mg, 1 mg and 100 mg, 1 mg and 50 mg, 1 mg and 25 mg, 1 mg and 10 mg, 5 mg and 100 mg, 5 mg and 50 mg, 5 mg and 25 mg, 5 mg and 15 mg, or 5 mg and 10 mg.

The MC4R agonist or composition thereof may be administered to a subject daily, weekly or monthly. In an embodiment, the MC4R agonist or composition thereof is administered daily, e.g., once daily, twice daily, or three times daily. In an embodiment, the MC4R agonist or composition thereof is administered weekly, e.g.,
5 once every week, once every two weeks, once every three weeks. In embodiments, the MC4R agonist or composition thereof is administered daily over a period of at least 3 weeks, e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2,
10 3, 4 years or more.

In embodiments, the method comprises administering the MC4R agonist or composition thereof in a unit dosage form suitable for injection, e.g., subcutaneous injection, to the subject. In embodiments, the unit dosage form is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe), an implantable device, a needleless hypodermic
15 injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system. In embodiments, the MC4R agonist is administered subcutaneously, e.g., by subcutaneous injection.

In embodiments, the subject is obese, e.g., severely obese. In embodiments, the subject has early onset severe obesity. In embodiments, the subject is
20 hyperphagic. In embodiments, the subject experiences severe hunger. In embodiments, the subject has a body mass index (BMI) greater than 25 kg/m² (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In
25 embodiments, the subject has a body mass index (BMI) greater than 35 kg/m² (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In embodiments, the subject has a body mass
30 index (BMI) greater than 40 kg/m² (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In

embodiments, the subject has a body mass index (BMI) greater than 45 kg/m² (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In embodiments, the subject has a BMI higher than the 85-95th percentile prior to administration of the MC4R agonist or composition thereof, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

In embodiments, the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist or composition thereof, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In embodiments, the subject has a lower body weight after administration of the MC4R agonist or composition thereof than before administration of the agonist.

In embodiments, administration of the MC4R agonist or composition thereof results in a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment. In embodiments, administration of the MC4R agonist or composition thereof results in a reduction of BMI by about 1%, 2%, 3%, 5%, 6%, 7%, 8%, 9%, 10%, or more, e.g., by at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 weeks or longer.

In embodiments, administration of the MC4R agonist or composition thereof results in no detectable/significant decrease in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days or longer, e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass).

In embodiments, administration of the MC4R agonist or composition thereof results in a reduction in food intake of at least 5 kcal/kg/day, e.g., 5, 10, 20, 30, 40, 50, 60, 70, 80, or 90 or more kcal/kg/day. In embodiments, the reduction in food intake is relative to the food intake at baseline. In embodiments, the baseline food intake is at least 100 kcal/kg/day, e.g., for a pediatric subject at about 1 year of age. In embodiments, the baseline food intake is at least 40 kcal/kg/day, e.g., for a pediatric subject, e.g., in late adolescence.

In embodiments, administration of the MC4R agonist or composition thereof results in a reduction in waist circumference of the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

5 In embodiments, administration of the MC4R agonist or composition thereof results in no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment. In embodiments, administration of the MC4R agonist or composition thereof results in a reduction in blood
10 pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment. In embodiments, administration of the MC4R agonist or composition thereof results in a reduction in systolic blood of the subject of at least 3 mmHg (e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more) compared to the blood pressure of
15 the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment. In embodiments, administration of the MC4R agonist or composition thereof results in a reduction in diastolic blood pressure of the subject of at least 4 mmHg (e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after
20 initiation of treatment.

In embodiments, administration of the MC4R agonist or composition thereof results in a reduction of hunger in a subject. The reduction of hunger may result in a reduction of food intake, decrease in resting energy expenditure (REE), reduction of weight, reduction in waist circumference, and/or reduction in blood pressure in the
25 subject.

In embodiments, the subject is a mammal, e.g., a human. In an embodiment, the subject is an adult (e.g., 18 years of age or older). In an embodiment, the subject is a pediatric subject, e.g., a child.

In embodiments, the method further comprises acquiring knowledge of the genotype
30 of the subject, e.g., acquiring knowledge of the genotype of an MC4R pathway agonizable

gene, e.g., a gene listed in Table 1. In embodiments, the knowledge is acquired directly, e.g., from a sample (e.g., a blood, serum, urine, or tissue (e.g., biopsy) sample) from the subject.

In embodiments, the MC4R agonist or composition thereof is administered in response to the detection of a predetermined sequence, e.g., a mutation, MC4R pathway agonizable gene, e.g., a gene listed in Table 1. In embodiments, the predetermined sequence, e.g., mutation, is detected in a nucleic acid by a method chosen from one or more of: a nucleic acid hybridization assay, an amplification-based assay, a PCR-RFLP assay, real-time PCR, sequencing (e.g., DNA sequencing, e.g., next generation sequencing or Sanger method sequencing, bisulfite sequencing, or pyrosequencing), screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC, or mass-spectrometric genotyping. In embodiments, the predetermined sequence, e.g., mutation, is detected in the subject. In embodiments, the predetermined sequence, e.g., mutation, is detected in a nucleic acid molecule or a polypeptide in a sample from the subject. In embodiments, the sample comprises cells from a blood, serum, urine, or tissue (e.g., biopsy) from the subject. In embodiments, the method comprises acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in a gene listed in

In some embodiments, the compound is a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is a compound of Formula (II) or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (II) is Hydantoin(C(O)-(Arg-Gly))-cyclo(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO:148) or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), is formulated as a pharmaceutical composition.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are

described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Other features, objects, and advantages of the disclosure will be apparent from the
5 description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph of the percent change in body mass index (BMI) from baseline of five subjects during a period of approximately five to eight months. These
10 subjects participated in a long-term extension study investigating the efficacy, safety, and tolerability of an exemplary MC4R agonist, SEQ ID NO: 140, for treatment of hypothalamic obesity.

DETAILED DESCRIPTION OF THE INVENTION

15 The present disclosure is based at least in part on the discovery that obesity, specifically a non-genetic obesity including hypothalamic obesity and other related disorders, may be treated in a subject by administering a therapeutic agent targeting the melanocortin 4 receptor (MC4R) pathway, e.g., an MC4R agonist. In an embodiment, the subject has hypothalamic obesity. In an embodiment, the subject has
20 been identified as having or diagnosed with hypothalamic obesity. In an embodiment, administering an MC4R agonist to a subject leads to significant weight loss, decrease in hunger, and/or an increase in energy expenditure in the subject. Exemplary MC4R agonists, as well as related formulations and methods of use are described in further detail herein.

25 Definitions

As used herein “about” and “approximately” generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

30 “Acquire” or “acquiring” as the terms are used herein, refer to obtaining possession of a physical entity, or a value, e.g., a numerical value, or knowledge of

(e.g., knowledge of the sequence or mutational state of) a genotype or a nucleic acid or polypeptide, by “directly acquiring” or “indirectly acquiring” the physical entity, value, or knowledge. “Directly acquiring” means performing a physical process (e.g., performing a synthetic or analytical method) to obtain the physical entity, value, or knowledge. “Indirectly

5 acquiring” refers to receiving the physical entity, value, or knowledge from another party or source (e.g., a third-party laboratory that directly acquired the physical entity, value, or knowledge). Directly acquiring a physical entity includes performing a process that includes a physical change in a physical substance, e.g., a starting material. Exemplary changes include making a physical entity from two or more starting materials, shearing or

10 fragmenting a substance, separating or purifying a substance, combining two or more separate entities into a mixture, performing a chemical reaction that includes breaking or forming a covalent or non-covalent bond. Directly acquiring a value or knowledge includes performing a process that includes a physical change in a sample or another substance. Examples include performing an analytical process which includes a physical change in a

15 substance, e.g., a sample, analyte, or reagent (sometimes referred to herein as “physical analysis”), performing an analytical method, e.g., a method which includes one or more of the following: separating or purifying a substance, e.g., an analyte, or a fragment or other derivative thereof, from another substance; combining an analyte, or fragment or other derivative thereof, with another substance, e.g., a buffer, solvent, or reactant; or changing the

20 structure of an analyte, or a fragment or other derivative thereof, e.g., by breaking or forming a covalent or non-covalent bond, between a first and a second atom of the analyte; or by changing the structure of a reagent, or a fragment or other derivative thereof, e.g., by breaking or forming a covalent or non-covalent bond, between a first and a second atom of the reagent.

25 As used herein, the term “functional,” as applied to an allele, e.g., of a MC4R pathway agonizable gene, refers to an allele having, e.g., at least 5, 10, 20, 30, 40, 50, 70, or 80% of the activity of a reference allele, e.g., a wildtype allele.

As used herein, the term “nonfunctional,” as applied to an allele, e.g., a MC4R pathway agonizable gene, refers to an allele which has less than 5, 10, 20, 30, 40, 50, 70, or

30 80% of the activity of a reference allele, e.g., a wildtype allele. In an embodiment, a nonfunctional allele is an allele of the gene that is other than a functional allele, as the term

functional allele is defined herein. By way of example, in an embodiment, if a functional allele has at least 20% of the activity of a reference allele a nonfunctional allele is an allele with less than 20% of the activity.

As used herein, the term “MC4R pathway agonizable gene” refers to a gene
5 associated with a phenotype which can be modulated, e.g., ameliorated or lessened, by modulating MC4R, e.g., agonizing MC4R, e.g., with an MC4R agonist. In an embodiment, the phenotype is hyperphagia, appetite, unwanted appetite, obesity, weight, body mass, or a metabolic syndrome (e.g., diabetes) and the phenotype is, e.g., modulated, e.g., reduced or ameliorated.

10 In an embodiment, the term “MC4R pathway agonizable gene” does not include the melanocortin 4 receptor (MC4R) gene. In an embodiment, the term “MC4R pathway agonizable gene” does not include POMC. In an embodiment, the MC4R pathway agonizable gene does not comprise any one of POMC, Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1, also called PC1/3), MAGE-like-2
15 (MAGEL2), leptin receptor (leptin-R), leptin, 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled (5-HT_{2c} receptor), nescient helix loop helix 2 (NHL2, also called NSCL2), pro-hormone convertase, carboxypeptidase E (CPE), and single-minded 1 (Sim1). In an embodiment, the MC4R pathway agonizable gene does not comprise any gene disclosed in WO2013/102047 or WO 2017/059076, the
20 full contents of each of which is incorporated herein by reference in its entirety.

In an embodiment, at least one of the MC4R alleles is functional, e.g., it has at least 5, 10, 20, 30, 40, 50, 70, or 80% of the activity of a reference allele, e.g., a wildtype allele, e.g., as measured by a functional assay. In an embodiment, one of the MC4R alleles is functional. In an embodiment, both MC4R alleles are functional. In
25 an embodiment, the subject is heterozygous at the MC4R gene and both alleles are functional. In an embodiment, the subject is homozygous at the MC4R gene for a functional allele.

In an embodiment, both MC4R alleles are nonfunctional. (A nonfunctional allele is an allele which is not functional, as functional is defined herein.) In an embodiment, the subject
30 is heterozygous at the MC4R gene and both alleles are nonfunctional. In an embodiment the subject is homozygous at the MC4R gene for a nonfunctional allele.

In an embodiment, at least one allele of an MC4R pathway agonizable gene other than MC4R is functional, e.g., it has at least 5, 10, 20, 30, 40, 50, 70, or 80% of the activity of a reference allele, e.g., a wildtype allele, e.g., as measured by a functional assay. In an embodiment one allele of an MC4R pathway agonizable gene other than MC4R is functional.

5 In an embodiment both alleles of an MC4R pathway agonizable gene other than MC4R are functional. In an embodiment the subject is heterozygous at an MC4R pathway agonizable gene other than MC4R and both alleles are functional. In an embodiment the subject is homozygous at an MC4R pathway agonizable gene other than MC4R for a functional allele.

In an embodiment, both MC4R alleles are nonfunctional. (A nonfunctional allele is an
10 allele which is not functional, as functional is defined herein.) In an embodiment the subject is heterozygous at the MC4R gene and both alleles are nonfunctional. In an embodiment the subject is homozygous at the MC4R gene for a nonfunctional allele.

In an embodiment, an epigenetic modification, e.g., a histone modification, e.g., acetylation or nucleobase methylation, e.g., cytosine methylation, is present and is associated
15 with the MC4R pathway agonizable gene phenotype, e.g., hyperphagia, appetite, unwanted appetite, obesity, weight, body mass, or a metabolic syndrome (e.g., diabetes)

In an embodiment, the epigenetic modification is associated with an MC4R pathway agonizable gene. In an embodiment, the epigenetic modification is associated with MC4R.

In an embodiment, the epigenetic modification is associated with an MC4R pathway
20 agonizable gene other than MC4R. In an embodiment, the MC4R pathway agonizable gene does not comprise any one of POMC, Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1, also called PC1/3), MAGE-like-2 (MAGEL2), leptin receptor (leptin-R), leptin, 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled (5-HT_{2c} receptor), nescient helix loop helix 2 (Nhlh2, also called NSCL2), pro-hormone convertase, carboxypeptidase
25 E (CPE), and single-minded 1 (Sim1). In an embodiment, the MC4R pathway agonizable gene does not comprise any gene disclosed in WO2013/102047 or WO 2017/059076, the full contents of each of which is incorporated herein by reference in its entirety. As used herein, the term “obese” refers to a subject having a body mass index (BMI) within the ranges defined as “obese” by the Center for Disease Control (*see*, e.g., URL.cdc.gov/obesity/defining.html and www.cdc.gov/obesity/childhood-/defining.html, last accessed on August
30 26, 2012) or as defined by “Clinical Guidelines on the Identification, Evaluation, and

Treatment of Overweight and Obesity in Adults” from the National Institutes of Health. BMI is obtained by dividing a subject’s weight, e.g., in kilograms (kg) by the square of the subject’s height, e.g., in meter (m). For example, an adult who has a BMI of 30 kg/m² or higher is considered obese. For example, an adult with a BMI of 25.0 to 29.9 kg/m² is considered overweight; an adult with a BMI of 18.5 to 24.9 kg/m² is considered to have a normal or healthy weight range; and an adult with a BMI of less than 18.5 kg/m² is considered to be underweight. For example, an adult having a height of 5 feet, 9 inches with a body weight of 203 pounds or more is considered obese. For pediatric subject, e.g., children and teens, obese refers to a subject having a BMI at or above the 85th to 95th percentile for pediatric subjects, e.g., children and teens, of the same age and sex.

As used herein, the term “BMI Z-Score” refers to the number of standard deviations in which the absolute BMI value diverges from the mean BMI of a population of interest. For example, a BMI Z-Score of +1.0 indicates that the subject BMI is one (1) standard deviation above the mean BMI (e.g., at approximately the 84th percentile of the population for BMI) of the population of interest. In an embodiment, the BMI Z-score of an obese pediatric patient is at or above a BMI Z-Score of +1.04 to +1.65 or greater, corresponding to a BMI at or above the 85th to 95th percentile for the pediatric subject relative to a population of pediatric subjects of the same age and sex.

As used herein, the terms “Impact of Weight on Quality of Life (IWQOL)” and “Impact of Weight on Quality of Life-Lite” refers to a psychometric questionnaire for obese and overweight subjects to assess the ramifications of obesity on the subject’s ability to live satisfactorily, wherein the scores are individually assessed by the subject or a guardian of the subject. In an embodiment, the IWQOL or IWQOL-Lite score diminishes when the subject develops hypothalamic obesity relative to a reference IWQOL or IWQOL-Lite score, e.g., the IWQOL or IWQOL-Lite score prior to developing hypothalamic obesity. In an embodiment, the IWQOL or IWQOL-Lite score increases after administration of a therapy which ameliorates the symptoms of hypothalamic obesity, relative to a reference IWQOL or IWQOL-

Lite score, e.g., the IWQOL or _IWQOL-Lite score prior to administration of the therapy.

As used herein, a “weekly average of daily most hunger score” refers to the average or mean of the daily most score hunger score of a subject for a period of week or seven days.

A “severely obese” subject or a subject having “severe obesity” refers to a subject
5 having a BMI of 35 kg/m² or higher, e.g., 40 kg/m² or higher. For example, a severely obese subject is over 100% over the ideal (normal, healthy) body weight.

As used herein “early onset”, e.g., as in early onset obesity, refers to an onset (e.g., first occurrence of one or more symptoms of a disorder, e.g., a disorder described herein, e.g., obesity) that occurs in a subject before adulthood, e.g., during childhood, e.g., when the
10 subject is less 18 years of age or younger (e.g., 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 year of age or younger, or during adolescence, e.g., when the child is younger than 12 years of age or when the child is younger than 6 years of age).

As used herein, the term “metabolic syndrome” refers to a group of symptoms that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes.
15 According to the American Heart Association and the National Heart, Lung, and Blood Institute, metabolic syndrome also referred to as Syndrome X) is present if a subject has three or more of the following signs: 1) Blood pressure equal to or higher than 130/85 mmHg; 2) Fasting blood sugar (glucose) equal to or higher than 100 mg/dL; 3) Large waist circumference (length around the waist): - Men - 40 inches or more; - Women - 35 inches or
20 more; 4) Low HDL cholesterol: - Men - under 40 mg/dL; - Women - under 50 mg/dL; 5) Triglycerides equal to or higher than 150 mg/dL. Metabolic syndrome can be diagnosed by testing subject’s blood pressure, blood glucose level, HDL cholesterol level, LDL cholesterol level, total cholesterol level, and triglyceride level.

As used herein, the term “agonist” refers to any chemical compound, either naturally
25 occurring or synthetic, that, upon interacting with (e.g., binding to) its target, e.g., MC4R, raises the signaling activity of MC4R above its basal level. An agonist can be a superagonist (*i.e.* a compound that is capable of producing a greater maximal response than the endogenous agonist for the target receptor, and thus has an efficacy of more than 100%), a full agonist (*i.e.* a compound that elicits a maximal response following receptor occupation
30 and activation) or a partial agonist (*i.e.* a compounds that can activate receptors but are unable to elicit the maximal response of the receptor system).

As used herein “treating” includes achieving one or more of the following results: reducing the body weight (as measured, for example, by a body mass index (BMI) and/or body weight), e.g., compared to a control (e.g., body weight before treatment or a predetermined body weight); reducing the waist circumference, e.g., compared to a control (e.g., waist circumference before treatment or a predetermined waist circumference); reducing the hunger level, e.g., compared to a control (e.g., hunger level before treatment or a predetermined hunger level); increasing the resting energy expenditure (REE), e.g., compared to a control (e.g., REE before treatment or a predetermined REE); decreasing the food intake, e.g., compared to a control level (e.g., before treatment or a predetermined food intake); ameliorating or improving a clinical symptom or indicators associated with a disorder described herein such as obesity, Prader Willi Syndrome, Smith-Magenis syndrome, e.g., type-II diabetes, pre-diabetic condition, blood level of hemoglobin A1C (Hb1Ac) above 6%, hyperinsulinemia, hyperlipidemia, insulin insensitivity, or glucose intolerance; delaying, inhibiting or preventing the progression of obesity and/or obesity related indications; or partially or totally delaying, inhibiting or preventing the onset or development of obesity or a obesity related indication. Delaying, inhibiting or preventing the progression of the obesity includes for example, delaying, inhibiting or preventing the progression of a subject having normal weight to obesity. In embodiments, a control is a value of a parameter measured before treatment by a MC4R agonist described herein or a predetermined value. The term “treating” further includes partially or totally reducing the risk for coronary artery disease, stroke, and type 2 diabetes associated with the metabolic syndrome as well as ameliorating or improving a clinical symptom or signs of metabolic syndrome associated with metabolic syndrome, such as any one or more of the five indicators listed above. For example, the term “treating” includes delaying, inhibiting or preventing the progression of parameters associated with the metabolic syndrome, including insulin resistance, glucose clearance and parameters of cardiovascular disease including heart rate and blood pressure.

As used herein “inhibition” or “inhibits” can include a reduction in a certain parameter, such as a parameter described herein. For example, inhibition of a parameter, e.g., activity, can be at least 5%, 10%, 20%, 30%, 40%, or more is included by this term. Thus, inhibition need not be 100%.

“Prophylactic treatment” refers to treatment before onset of obesity to prevent, inhibit or reduce its occurrence.

As used herein, the term “subject” refers to a mammal, e.g., a human. Subject can also refer to an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). In an embodiment, the subject is a pediatric subject (e.g., a subject under 21 or 18 years of age). In an embodiment, the subject is an adult subject (e.g., a subject over 18 or 21 years of age).

As used herein, the term “mutation” can refer to an altered nucleic acid sequence of a gene or fragment thereof compared to a wild-type sequence. For example, a mutation can include a point mutation, frame-shift mutation, missense mutation, inversion, deletion, insertion, truncation, chromosomal translocation. In embodiments, a mutation can result in the gene or fragment thereof coding for a non-functional protein, a protein with reduced activity (or a partially functional protein), or a protein with altered activity. For example, a “loss of function” mutation refers to a mutation that results in the gene or fragment thereof coding for a non-functional protein, which has substantially reduced activity compared to its wild-type counterpart (e.g., a non-functional protein has less than 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less activity than its wild-type counterpart). For example, “partial loss of function” mutation refers to a mutation that results in the gene or fragment thereof coding for a partially functional protein, which has reduced activity compared to its wild-type counterpart (e.g., a partially functional protein has less than 50% and greater than 10% of the activity of its wild-type counterpart).

As used herein “heterozygous” refers to the presence of two different alleles (having different nucleic acid sequences) for a given gene in a subject. In some embodiments, “heterozygous mutation” can refer to the presence of a mutation on one allele for a given gene and the lack of a mutation on the other allele of the same gene in a subject (e.g., one mutant allele and one wild type allele for a given gene). In other embodiments, a “heterozygous mutation” can be a “compound heterozygous” mutation, which refers to the presence of a mutation (e.g., loss of function mutation or partial loss of function mutation) on one allele for a given gene and a different (e.g., loss of function mutation or partial loss of function mutation) on the other allele for the same gene (e.g., two different alleles that are

both mutated, e.g., non-functional or partially functional). In embodiments, where a compound heterozygous mutation includes two non-functional alleles, the genotype can be a null genotype or functionally deficient genotype.

As used herein “homozygous” refers to the presence of two identical alleles for a given gene. In some embodiments, a “homozygous mutation” refers to the presence of two mutant alleles for a given gene, where the two mutant alleles are identical.

As used herein “null genotype” refers to the presence of two non-functional alleles of a gene in a subject.

As used herein “unit dosage form” refers to a physically discrete unit suited as unitary doses for a subject to be treated. Each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

As used herein “dosage” refers to a quantity or amount of a therapeutic agent. In some embodiments, a dosage is the amount administered to the subject in a single administration, e.g., in a single injection, a single infusion, or single administration of one or more unit dosages. In embodiments, a dosage is the amount administered to the subject in multiple administrations, e.g., multiple injections, multiple infusions, or multiple administrations of one or more unit dosages. In other embodiments, a dosage can refer to the total amount administered to the subject in a certain time period, e.g., per day. In such examples, the dosage is typically referred to as “daily dosage” or dosage in terms of quantity per day.

As used herein “hunger” or “hunger level” refers to a subject’s appetite, desire to consume food, or perceived need for food. In embodiments, the hunger or hunger level of a subject can be quantified by using a scale to obtain a hunger score. In embodiments, the scale for hunger assigns a higher score for a subject that more frequently (e.g., often or always) feels unbearable hunger and a lower score for a subject that less frequently (e.g., sometimes or never) feels unbearable hunger. See, e.g., Sibilio. *Psychological Topics* 19 (2010), 2, 341-354. For example, a Likert scale for hunger can be used that assigns scores from 0 to 10 points (0=no hunger; 10=severe hunger). In other examples, a Likert scale for hunger can be used that

assigns scores from 1 to 4 points, where a subject who never feels unbearable hunger is assigned a score of 1, where a subject who sometimes feels unbearable hunger is assigned a score of 2, where a subject who often feels unbearable hunger is assigned a score of 3, and where a subject who always feels unbearable hunger is assigned a score of 4. See *Id.*

5

Selected Chemical Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. Where the amino acid has D and L isomeric forms, it is the L form of the amino acid that is represented unless otherwise explicitly indicated.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C₁-C₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₃-C₆, C₃-C₅, C₃-C₄, C₄-C₆, C₄-C₅, and C₅-C₆ alkyl.

The compounds useful for practicing the methods described herein may possess one or more chiral centers and so exist in a number of stereoisomeric forms. All stereoisomers

and mixtures thereof are included in the scope of the present disclosure. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilizing methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of the disclosure.

The compounds useful for practicing the methods described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

The term "pharmaceutically acceptable salt" as used herein is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds used in the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds used in the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, e.g., Berge et al, *Journal of Pharmaceutical Science* 66: 1-19 (1977)). Certain specific compounds used in the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. These salts may be prepared by methods known to those skilled in the art. Other

pharmaceutically acceptable carriers known to those of skill in the art are suitable for use in the present disclosure.

The compounds useful for practicing the methods described herein can also exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. The compounds useful for practicing the methods described herein may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

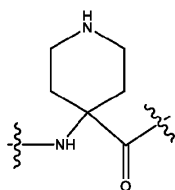
The term “solvate” refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates.

The term “hydrate” refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x H_2O$, wherein R is the compound and wherein x is a number greater than 0.

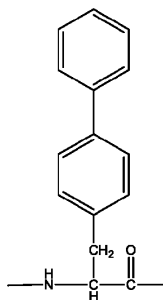
The term “tautomer” as used herein refers to compounds that are interchangeable forms of a compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest. Table 1 provides definition for chemical abbreviations used herein. Table 1. Definitions of chemical abbreviations.

Symbol	Meaning
Abu	α -aminobutyric acid

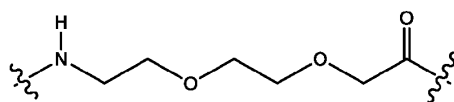
Ac	acyl group
Acc	1-amino-1-cyclo(C ₃ -C ₉)alkyl carboxylic acid
A3c	1-amino-1cyclopropanecarboxylic acid
A4c	1-amino-1-cyclobutanecarboxylic acid
A5c	1-amino-1-cyclopentanecarboxylic acid
A6c	1-amino-1-cyclohexanecarboxylic acid
Aha	7-aminoheptanoic acid
Ahx	6-aminohexanoic acid
Aib	α -aminoisobutyric acid
Aic	2-aminoindan-2-carboxylic acid
Ala or A	Alanine
β -Ala	β -alanine
Apc	denotes the structure:



Apn	5-aminopentanoic acid (HN—(CH ₂) ₄ —C(O))
Arg or R	Arginine
hArg	Homoarginine
Asn or N	Asparagine
Asp or D	aspartic acid
Bal	3-benzothienylalanine
Bip	4,4'-biphenylalanine, represented by the structure

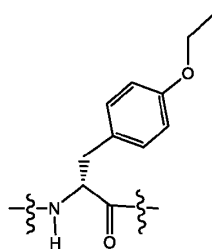


Bpa	4-benzoylphenylalanine
4-Br-Phe	4-bromo-phenylalanine
Cha	β -cyclohexylalanine
hCha	homo-cyclohexylalanine
Chg	Cyclohexylglycine
Cys or C	Cysteine
hCys	Homocysteine
Dab	2,4-diaminobutyric acid
Dap	2,3-diaminopropionic acid
Dip	β,β -diphenylalanine
Doc	8-amino-3,6-dioxaoctanoic acid with the structure of:



2-Fua	β -(2-furyl)-alanine
Gaba	4-aminobutyric acid
Gln or Q	Glutamine
Glu or E	glutamic acid
Gly or G	Glycine
His or H	Histidine
3-Hyp	trans-3-hydroxy-L-proline, i.e., (2S,3S)-3-hydroxy-pyrrolidine-2-carboxylic acid
4-Hyp	4-hydroxyproline, i.e., (2S,4R)-4-hydroxypyrrolidine-2-carboxylic acid
Ile or I	Isoleucine
Leu or L	Leucine
hLeu	Homoleucine
Lys or K	Lysine
Met or M	Methionine
β -hMet	β -homomethionine
1-Nal	β -(1-naphthyl)alanine
2-Nal	β -(2-naphthyl)alanine

Nip	nipecotic acid
Nle	Norleucine
Ole	octahydroindole-2-carboxylic acid
Orn	Ornithine
2-Pal	β -(2-pyridyl)alanine
3-Pal	β -(3-pyridyl)alanine
4-Pal	β -(4-pyridyl)alanine
Pen	Penicillamine
Pff	(S)-pentafluorophenylalanine
Phe or F	Phenylalanine
hPhe	homophenylalanine
Pro or P	Proline
hProP	Homoproline
Ser or S	Serine
Tle	tert-Leucine
Taz	β -(4-thiazolyl)alanine
2-Thi	β -(2-thienyl)alanine
3-Thi	β -(3-thienyl)alanine
Thr or T	Threonine
Trp or W	Tryptophan
Tyr or Y	Tyrosine
D-(Et) Tyr	has a structure of



Val or V Valine

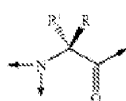
Certain other abbreviations used herein are defined as follows:

Boc:	tert-butyloxycarbonyl
Bzl:	Benzyl
DCM:	Dichloromethane
DIC:	N,N-diisopropylcarbodiimide
DIEA:	diisopropylethyl amine
Dmab:	4-{N-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-amino}benzyl
DMAP:	4-(dimethylamino)pyridine
DMF:	Dimethylformamide
DNP:	2,4-dinitrophenyl
Fm:	Fluorenylmethyl
Fmoc:	fluorenylmethyloxycarbonyl
For:	Formyl
HBTU:	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
cHex	Cyclohexyl
HOAT:	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt:	1-hydroxy-benzotriazole
MBNA	4-methylbenzhydramine
Mmt:	4-methoxytrityl
NMP:	N-methylpyrrolidone
O-tBu	oxy-tert-butyl
Pbf:	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
tBu:	tert-butyl
TIS:	triisopropylsilane
TOS:	Tosyl
Trt	Trityl
TFA:	trifluoro acetic acid
TFFH:	tetramethylfluorophosphonium hexafluorophosphate

Z: benzyloxycarbonyl

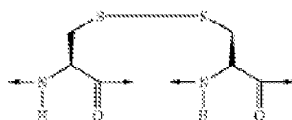
Unless otherwise indicated, with the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-C(R)(R')-CO-, wherein R and R' each is, independently, hydrogen or the side chain of an amino acid (e.g., R=CH₃ and R'=H for Ala), or R and R' may be joined to form a ring system.

For the N-terminal amino acid, the abbreviation stands for the structure of:

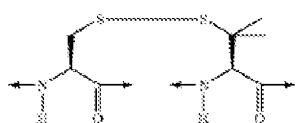


The designation "NH₂" in e.g., as in Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO:13), indicates that the C-terminus of the peptide is amidated. Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys) (SEQ ID NO:107), or alternatively Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH (SEQ ID NO:107), indicates that the C-terminus is the free acid.

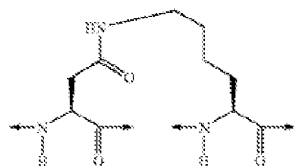
"-c(Cys-Cys)-" or "-cyclo(Cys-Cys)-" denotes the structure:



"-c(Cys-Pen)-" or "-cyclo(Cys-Pen)-" denotes the structure:

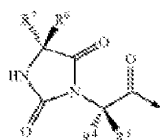


"-c(Asp-Lys)-" or "-cyclo(Asp-Lys)-" denotes the structure:

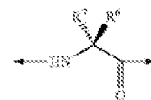


The following abbreviations are used throughout the disclosure:

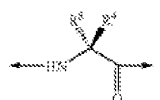
“Hydantoin-(C(O)-(A^a-A^b))” denotes the structure:



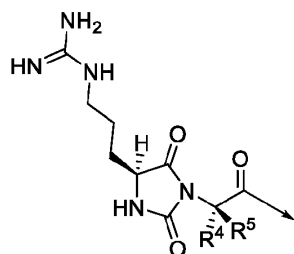
, wherein amino acid “A^a” has the structure:



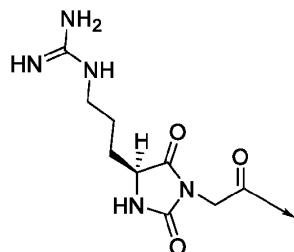
and amino acid “A^b” the structure:



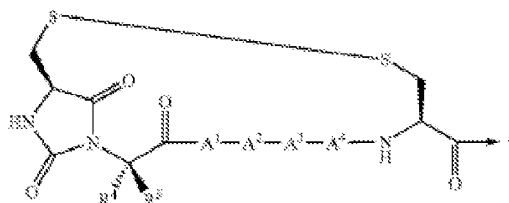
5 For example, “Hydantoin-(C(O)-(Arg-A^b))” would have the following structure:



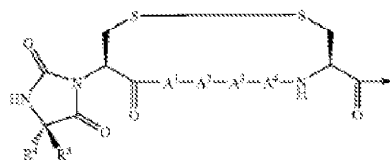
For example, “Hydantoin-(C(O)-(Arg-Gly))” would have the following structure:



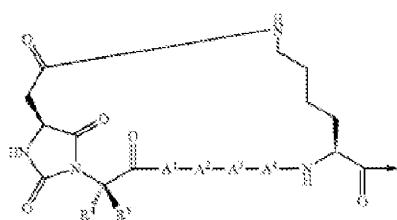
10 For example, a compound represented as “c[Hydantoin(C(O)-(Cys-A^b))-A¹-A²-A³-A⁴-Cys]-” would have the following the structure:



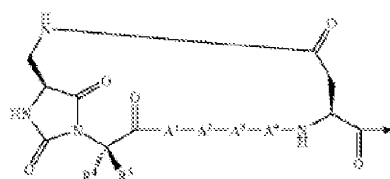
whereas a compound represented as “c[Hydantoin(C(O)-(A^b-Cys))-A¹-A²-A³-A⁴-Cys]-” would have the structure:



For further guidance, “c[Hydantoin(C(O)-(Asp-A^b))-A¹-A²-A³-A⁴-Lys]-” represents
5 the following compound:



whereas “c[Hydantoin(C(O)-(Dap-A^b))-A¹-A²-A³-A⁴-Asp]-” has the following
formula:



10 “Acyl” refers to R^{''}-C(O)-, where R^{''} is H, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkenyl, substituted alkenyl, aryl, alkylaryl, or substituted alkylaryl, and is indicated in the general formula of a particular embodiment as “Ac”.

“Alkyl” refers to a hydrocarbon group containing one or more carbon atoms, where multiple carbon atoms if present are joined by single bonds. The alkyl hydrocarbon group
15 may be straight-chain or contain one or more branches or cyclic groups.

“Hydroxyalkyl” refers to an alkyl group wherein one or more hydrogen atoms of the hydrocarbon group are substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

“Substituted alkyl” refers to an alkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, amine (e.g., -NH₂, -NHCH₃), -NO₂, guanidine, urea, amidine, and -(C₁-C₂₀) alkyl, wherein
5 said -(C₁-C₂₀) alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, —CF₃, —OCH₃, —OCF₃, and -(CH₂)₀₋₂₀-COOH. In different embodiments 1, 2, 3 or 4 substituents are present. The presence of -(CH₂)₀₋₂₀-COOH results in the production of an alkyl acid. Non-limiting examples of alkyl acids containing, or consisting of, -(CH₂)₀₋₂₀-COOH include 2-
10 norbornane acetic acid, tert-butyric acid, 3-cyclopentyl propionic acid, and the like.

The term “halo” encompasses fluoro, chloro, bromo and iodo.

Guanidines are a group of organic compounds that share a common functional group with the general structure (R¹R²N)(R³R⁴N)C=N-R⁵. The central bond within this group is an imine, and the group is related structurally to amidines and ureas.

15 “Heteroalkyl” refers to an alkyl wherein one or more of the carbon atoms in the hydrocarbon group is replaced with one or more of the following groups: amino, amido, —O—, —S— or carbonyl. In different embodiments 1 or 2 heteroatoms are present.

“Substituted heteroalkyl” refers to a heteroalkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group
20 consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, —CN, —SH, —NH₂, —NHCH₃, —NO₂, and -(C₁-C₂₀) alkyl, wherein said -(C₁-C₂₀) alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, —CF₃, -OCH₃, -OCF₃, and -(CH₂)₀₋₂₀-COOH. In different embodiments 1, 2, 3 or 4 substituents are present.

25 “Alkenyl” refers to a hydrocarbon group made up of two or more carbons where one or more carbon-carbon double bonds are present. The alkenyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups.

“Substituted alkenyl” refers to an alkenyl wherein one or more hydrogens are replaced with one or more substituents selected from the group consisting of halogen (i.e.,
30 fluorine, chlorine, bromine, and iodine), —OH, —CN, —SH, —NH₂, —NHCH₃, —NO₂, and -(C₁-C₂₀) alkyl, wherein said -(C₁-C₂₀) alkyl optionally may be substituted with one or

more substituents selected, independently for each occurrence, from the group consisting of halogens, $-\text{CF}_3$, $-\text{OCH}_3$, $-\text{OCF}_3$, and $-(\text{CH}_2)_{0-20}-\text{COOH}$. In different embodiments 1, 2, 3 or 4 substituents are present.

“Aryl” refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to three conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups. Preferably, the aryl is a 5- or 6-membered ring. Preferred atoms for a heterocyclic aryl are one or more sulfur, oxygen, and/or nitrogen. Non-limiting examples of aryl include phenyl, 1-naphthyl, 2-naphthyl, indole, quinoline, 2-imidazole, 9-anthracene, and the like. Aryl substituents are selected from the group consisting of $-(\text{C}_1-\text{C}_{20})$ alkyl, $-(\text{C}_1-\text{C}_{20})$ alkoxy, halogen (i.e., fluorine, chlorine, bromine, and iodine), $-\text{OH}$, $-\text{CN}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-(\text{C}_1-\text{C}_{20})$ alkyl substituted with halogens, $-\text{CF}_3$, $-\text{OCF}_3$, and $-(\text{CH}_2)_{0-20}-\text{COOH}$. In different embodiments the aryl contains 0, 1, 2, 3, or 4 substituents.

“Alkylaryl” refers to an “alkyl” joined to an “aryl”.

The term “ (C_{1-12}) hydrocarbon moiety” encompasses alkyl, alkenyl and alkynyl and in the case of alkenyl and alkynyl there is C_2-C_{12} .

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different. For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

Designation “(amino acid)_n” means that an amino acid is repeated *n* times. For example, designation “(Pro)₂” or “(Arg)₃” mean that proline or arginine residues are repeated, respectively, two or three times.

MC4R

hMC4R is a protein encoded by a genomic sequence having GenBank accession number CH471077.2. Mutations in the MC4R receptor are an associated cause of severe childhood obesity. The carrier prevalence for MC4R mutations in a juvenile-onset obese population has been noted to be around 2.5% with a highest

prevalence of 6% among severely obese children. Humans with MC4R mutations show a more or less similar phenotype as has been described for mice with mutations in the MC4R gene. MC4R deficient patients show hyperphagia, hyperinsulinaemia, increased fat mass, accompanied by lean body mass, bone mineral density and linear growth rate increases, with
5 no changes in cortisol levels, gonadotropin, thyroid and sex steroid levels. In contrast to MC4R deletion, hyperphagia and hyperinsulinaemia tends to subside with age in human subjects. Similar to the MC4R knockout mice, the phenotype in heterozygote carriers is intermediate in comparison to homozygote carriers. The exhibited hyperphagia observed upon a test meal is less severe than that observed in people with a leptin deficiency. The
10 severity of MC4R dysfunction seen in assays in vitro can predict the amount of food ingested at a test meal by the subject harboring that particular mutation and correlates with the onset and severity of the obese phenotype. At least 90 different MC4R mutations have been associated with obesity and additional mutations in the MC4R are likely to be discovered, leading to a similar obesity phenotype.

15 Examples of the MC4R mutations that cause obesity in humans are described, e.g., in Farooqi *et al.*, *The Journal of Clinical Investigation*, July 2000, vol. 106 (2), pp. 271-279 and Vaisse *et al.*, *The Journal of Clinical Investigation*, July 2000, vol. 106(2), pp. 253-262, the relevant portions of which are incorporated herein by reference).

Additional mutations that potentially cause obesity in humans include, R18H, R18L,
20 S36Y, P48S, V50M, F51L, E61K, I69T, D90N, S94R, G98R, I121T, A154D, Y157S, W174C, G181D, F202L, A219 V, I226T, G231S, G238D, N240S, C271R, S295P, P299L, E308K, I317V, L325F, and 750DelGA, as described in Xiang *et al.*, "Pharmacological characterization of 30 human melanocortin-4 receptor polymorphisms with the endogenous proopiomelanocortin-derived agonists, synthetic agonists, and the endogenous agouti-related
25 protein antagonist." *Biochemistry*, 2010 Jun 8; 49(22):4583-600, the relevant portions of which are incorporated herein by reference.

Further examples of mutations that potentially cause obesity in humans are those listed in Online Mendelian Inheritance in Man (OMIM), a database of human genes and genetic disorders, under the accession number 155541 (MC4R) (more precisely, accession
30 nos. 155541.0001-155541.0023) at the URL <http://omim.org/entry/155541>. Representative examples include 4-BP DEL, NT631; 4-BP INS, NT732; TYR35TER; ASP37VAL;

SER58CYS; ILE102SER; ASN274SER; 1-BP INS, 112A; 4-BP DEL, 211CTCT; ILE125LYS; ALA175THR; ILE316SER; TYR287TER; ASN97ASP; 15-BP DEL (delta88-92 codons); and SER127LEU. The relevant portions of the OMIM database are incorporated herein by reference. Additional exemplary mutations in MC4R are described in Lee. *Annals Acad. Med.* 38.1(2009):34-44.

In example embodiments, the MC4R mutation results in retention of the MC4R signaling activity. Mutations in the genomic sequence encoding MC4R can be detected by the methods that are known to a person of ordinary skill in the art. For example, the genomic sequence can be cloned using nucleotide primers, such as *e.g.*, the primers described in Farooqi *et al.*, *The Journal of Clinical Investigation*, July 2000, vol. 106 (2), pp. 271-279 and Vaisse *et al.*, *The Journal of Clinical Investigation*, July 2000, vol. 106(2), pp. 253-262, and the cloned sequence analyzed using commercially available sequencers and software.

Activity of MC4R can be measured by the methods known to a person of ordinary skill in the art. For example, cells can be transiently transfected with the cloned MC4R DNA, the transfected cells contacted by an agonist of MC4R (*e.g.* α -MSH), and the intracellular level of cAMP, the secondary messenger of MC4R, measured by an electrochemiluminescence assay described, *e.g.*, in Roubert *et al.*, *Journal of Endocrinology* (2010) 207, pp. 177-183. A reduction in MC4R signaling can be ascertained by comparing the intracellular level of cAMP produced in response to a given agonist by a wild type MC4R to that produced by a mutant MC4R.

The MC4R agonist may bind to the MC4R directly or indirectly. In an embodiment, the MC4R agonist binds to the MC4R in or near the ligand-binding pocket. In an embodiment, the MC4R agonist binds to the MC4R in or near the G-protein binding cavity. In an embodiment, the MC4R agonist binds to the MC4R binds in or near a transmembrane domain or extracellular loop, for example, TM2, TM3, TM5, TM7, EL2, and/or EL3. Additional interactions of the MC4R agonist and the MC4R may be exemplified in *Nat Cell Research* (2021) 31:1176-1189, which is incorporated herein by reference in its entirety.

Melanocortin-4 Receptor (MC4R) pathway genes

The melanocortin system, which includes melanocortins (MCs), agouti, agouti-related proteins, and their receptors, integrate hormonal, metabolic, and neural signals in order to control energy homeostasis and regulate appetite, energy expenditure, and body weight. The MCs, which include alpha-melanocyte-stimulating hormone (α -MSH), β -MSH, γ -MSH, and ACTH, are a family of peptide hormones that are derived from a precursor protein called pro-opiomelanocortin (POMC). Activation of MC4 receptor (MC4R) in the POMC-MC4R pathway increases energy expenditure and decreases food intake. See, e.g., Fan et al. Nature 1997;385:165-68. The POMC-MC4R pathway includes a number of proteins, such as melanocortins (MCs), MC4 receptor (MC4R), POMC, Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1, also called PC1/3), MAGE-like-2 (MAGEL2), leptin receptor (leptin-R), leptin, 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled (5-HT2c receptor), nescient helix loop helix 2 (NHL2, also called NSCL2), pro-hormone convertase, carboxypeptidase E (CPE), and single-minded 1 (Sim1), that together contribute to the regulation of energy homeostasis, e.g., by regulating appetite and energy expenditure. MC4R and other components of the POMC-MC4R pathway have a significant role in weight regulation. A mutation of the MC4R gene was reported to result in early-onset and severe obesity. It is believed that other genetic defects in the POMC-MC4R pathway likely also lead to early-onset and severe obesity. These genes are collectively termed "MC4R pathway agonizable genes" and examples are provided below. In an embodiment, the MC4R pathway agonizable gene does not comprise any one of POMC, Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1, also called PC1/3), MAGE-like-2 (MAGEL2), leptin receptor (leptin-R), leptin, 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled (5-HT2c receptor), nescient helix loop helix 2 (NHL2, also called NSCL2), pro-hormone convertase, carboxypeptidase E (CPE), and single-minded 1 (Sim1). In an embodiment, the subject does not exhibit a genetic mutation or genetic defect in an MC4R agonizable gene, e.g., an MC4R agonizable gene described below.

ADP Ribosylation Factor-like GTPase 6 (ARL6)

ADP Ribosylation Factor-like GTPase 6 (ARL6), also known as BBS3, is a member of the ARF-like (ADP ribosylation factor-like) sub-family of the ARF family of GTP-binding proteins, which are involved in the regulation of intracellular traffic. ARL6 is involved in

membrane protein trafficking at the base of the ciliary organelle and mediates recruitment onto plasma membrane of the BBSome complex. Together with BBS1, ARL6 is necessary for correct trafficking of PKD1 to primary cilia. Together with the BBSome complex and LTZL1, ARL6 controls SMO ciliary trafficking and contributes to the sonic hedgehog (SHH) pathway regulation. It is believed that ARL6 may regulate cilia assembly and disassembly and subsequent ciliary signaling events such as the Wnt signaling cascade. ARL6 isoform 2 may be required for proper retinal function and organization. A vision-specific transcript, encoding long isoform BBS3L, has also been described.

Mutations in the ARL6 gene are associated with Bardet-Biedl syndrome (BBS), a genetically heterogeneous disorder. BBS is a form of Laurence-Moon-Beidl syndrome and is characterized by obesity, retinopathy, learning disability, polydactyly, hypogenitalism, and retinitis pigmentosa 55. (See, e.g., Young et al. Am. J. Med. Genet. 78(5):461-7 (2002)).

The human ARL6 gene sequence is provided in GenBank Accession No. NG_008119.2, incorporated herein by reference. An exemplary human ARL6 nucleic acid sequence is provided in GenBank Accession No. NM_001278293.3, incorporated herein by reference. An exemplary amino acid sequence of human ARL6 is provided by Q9H0F7, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the ARL6 gene.

Retinoic Acid Induced 1 (RAI1)

Retinoic Acid Induced 1 (RAI1) is a transcription factor that regulates the circadian clock components: CLOCK, ARNTL/BMAL1, ARNTL2/BMAL2, PER1/3, CRY1/2, NR1D1/2, and RORA/C. RAI1 positively regulates the transcriptional activity of CLOCK, a core component of the circadian clock. (See, e.g., Williams et al. Am. J. Hum. Genet. 90(6):941-9 (2012)). RAI1 also regulates transcription through chromatin remodeling by interacting with other proteins in chromatin as well as proteins in the basic transcriptional machinery. It is believed that RAI1 may be important for embryonic and postnatal development and may be involved in neuronal differentiation.

Mutations in RAI1 (e.g., leading to haploinsufficiency) are associated with Smith-Magenis Syndrome, a disorder characterized by cognitive and behavioral abnormalities, including self-injurious behaviors and sleep disturbance, obesity, and distinct craniofacial

and skeletal anomalies, that has been associated with deletions involving chromosome 17p11.2. (*See, e.g.,* Slager et al. Nat Genet. 33(4):466-468 (2003)).

The human RAI1 gene sequence is provided in GenBank Accession No. NG_007101.2, incorporated herein by reference. An exemplary human RAI1 nucleic acid sequence is provided in GenBank Accession No. NM_030665.4, incorporated herein by reference. An exemplary amino acid sequence of human RAI1 is provided by Q7Z5J4-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the RAI1 gene.

Steroid Receptor Coactivator 1 (SRC1)

10 Steroid Receptor Coactivator 1 (SRC1), also known as Nuclear Receptor Coactivator 1 (NCOA1), is a transcriptional coactivator for steroid and nuclear hormone receptors. SRC1 is a member of the p160/SRC family, and like other family members, has histone acetyltransferase activity and contains a nuclear localization signal, as well as bHLH and PAS domains. SRC1 binds nuclear receptors directly and stimulates the transcriptional activities in a hormone-dependent fashion. SRC1 is involved in the coactivation of different nuclear receptors, such as for steroids, retinoids, thyroid hormone, and prostanoids. SRC1 is also involved in coactivation mediated by STAT3, STAT5A, STAT5B, and STAT6 transcription factors. SRC1 plays a central role in creating multi-subunit coactivator complexes that act via remodeling of chromatin, and possibly acts by participating in both chromatin remodeling and recruitment of general transcription factors. It is required with NCOA2 to control energy balance between white and brown adipose tissues and for mediating steroid hormone response. Alternatively spliced transcript variants encoding different isoforms have also been identified.

25 Mutations in SRC1 has been linked to obesity. Without wishing to be bound by theory, it is believed that SRC-1 modulates the function of hypothalamic Pro-opiomelanocortin (Pomc) neurons, which regulate food intake and body weight. Rare heterozygous variants of SRC1 were found in severely obese individuals that impaired leptin mediated Pomc reporter activity in cells. (*See, e.g.,* Yang et al. Nat. Commun. 10(1):1718 (2019)).

30 The human SRC1 gene sequence is provided in GenBank Accession No. NG_029014.2, incorporated herein by reference. An exemplary human SRC1 nucleic acid

sequence is provided in GenBank Accession No. NM_003743.5, incorporated herein by reference. An exemplary amino acid sequence of human SRC1 is provided by Q15788-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the SRC1 gene.

5 *Bardet-Biedl Syndrome 19 (BBS19)*

Bardet-Biedl Syndrome 19 (BBS19), also known as intraflagellar transport protein 27 homolog (IFT27), is a small GTPase-like component of the intraflagellar transport complex B, which is essential for cilia biogenesis and maintenance. BBS19 promotes the exit of the BBSome complex from cilia via its interaction with ARL6. BBS19 forms a subcomplex
10 within the IFT complex B with IFT25 and prevents aggregation of GTP-free ARL6 but is not believed to be involved in entry of the BBSome complex into cilium. (*See, e.g.,* Liew et al. Dev. Cell 31(3):265-278 (2014)). BBS19 is also required for hedgehog signaling. Its role in intraflagellar transport is mainly seen in tissues rich in ciliated cells such as kidney and testis. BBS19 is essential for male fertility, spermiogenesis and sperm flagella formation, plays a
15 role in the early development of the kidney, and may be involved in the regulation of ureteric bud initiation.

Mutations in the BBS19 gene have been associated with Bardet-Biedl syndrome (*See, e.g.,* Aldahmesh et al. Hum. Mol. Genet. 23(12):3307-15 (2014)).

The human BBS19 gene sequence is provided in GenBank Accession No. NG_034205.1, incorporated herein by reference. An exemplary human BBS19 nucleic acid
20 sequence is provided in GenBank Accession No. NM_001177701.3, incorporated herein by reference. An exemplary amino acid sequence of human BBS19 is provided by Q9BW83-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the BBS19 gene.

25 *Bardet-Biedl Syndrome 21 (BBS21)*

The Bardet-Biedl syndrome 21 (BBS21) gene, also known as chromosome 8 open reading frame 37 (C8orf37), encodes a broadly expressed protein of unknown function. High levels of BBS21 mRNA can be found in the brain, heart, and retina. The protein has been shown to co-localize with polyglutamylated tubulin at the base of the primary cilium in
30 human retinal pigment epithelial cells. Mutations in the BBS21 gene have been associated

with Bardet-Biedl syndrome, autosomal recessive cone-rod dystrophy (arCRD), and retinitis pigmentosa (*See, e.g.,* Heon et al. Hum. Mol. Genet. 25(11):2283-2294 (2016)).

The human BBS21 gene sequence is provided in GenBank Accession No. NG_032804.1, incorporated herein by reference. An exemplary human BBS21 nucleic acid sequence is provided in GenBank Accession No. NM_177965.4, incorporated herein by reference. An exemplary amino acid sequence of human BBS21 is provided by Q96NL8-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the BBS21 gene.

Centrosomal Protein 290 (CEP290)

Centrosomal Protein 290 (CEP290), also known as BBS14, encodes a protein with thirteen putative coiled-coil domains, a region with homology to SMC chromosome segregation ATPases, six KID motifs, three tropomyosin homology domains, and an ATP/GTP binding site motif A. The protein is localized to the centrosome and cilia and has sites for N-glycosylation, tyrosine sulfation, phosphorylation, N-myristoylation, and amidation.

CEP290 is involved in early and late steps in cilia formation and its association with CCP110 is required for inhibition of primary cilia formation by CCP110. CEP290 may play a role in early ciliogenesis in the disappearance of centriolar satellites and in the transition of primary ciliary vesicles (PCVs) to capped ciliary vesicles (CCVs). CEP290 is also required for the centrosomal recruitment of RAB8A and for the targeting of centriole satellite proteins to centrosomes such as of PCM1. It is required for the correct localization of ciliary and phototransduction proteins in retinal photoreceptor cells and may play a role in ciliary transport processes. Required for efficient recruitment of RAB8A to primary cilium. In the ciliary transition zone, CEP290 is part of the tectonic-like complex, which is required for tissue-specific ciliogenesis and may regulate ciliary membrane composition. CEP290 is involved in regulation of the BBSome complex integrity, specifically for presence of BBS2, BBS5, and BBS8/TTC8 in the complex, and in ciliary targeting of selected BBSome cargos. CEP290 may play a role in controlling entry of the BBSome complex to cilia.

Mutations in this gene have been associated with several ciliopathies including Bardet-Biedl syndrome, isolated retinal degeneration, nephronophthisis (NPHP), Joubert syndrome, Senior-Loken syndrome (SLSN), and neonatal lethal Meckel-Gruber syndrome

(MKS). (See, e.g., Zhang et al. Hu. Mol. Genet. 23(1):40-51 (2014) and Leitch et al. Nat. Genet. 40(4):443-448 (2008)).

The human CEP290 gene sequence is provided in GenBank Accession No. NG_008417.2, incorporated herein by reference. An exemplary human CEP290 nucleic acid sequence is provided in GenBank Accession No. NM_025114.4, incorporated herein by reference. An exemplary amino acid sequence of human CEP290 is provided by O15078-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the CEP290 gene.

Intraflagellar Transport 74 (IFT74)

Intraflagellar Transport 74 (IFT74) is a core component of the intraflagellar transport (IFT), a multi-protein complex involved in the transport of ciliary proteins along axonemal microtubules. IFT proteins are found at the base of the cilium as well as inside the cilium, where they assemble into long arrays between the ciliary base and tip. Specifically, IFT74, together with IFT81, forms a tubulin-binding module that specifically mediates transport of tubulin within the cilium. IFT74 binds beta-tubulin via its basic region and is required for ciliogenesis.

Naturally occurring mutations in this gene are associated with Bardet-Biedl Syndrome and amyotrophic lateral sclerosis--frontotemporal dementia. (See, e.g., Lindstrand et al. Am. J. Hum. Genet. 99(2):318-336 (2016)).

The human IFT74 gene sequence is provided in GenBank Accession No. NG_053083.1, incorporated herein by reference. An exemplary human IFT74 nucleic acid sequence is provided in GenBank Accession No. NM_001099222.2, incorporated herein by reference. An exemplary amino acid sequence of human IFT74 is provided by Q96LB3-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the IFT74 gene.

Leucine Zipper Transcription Factor Like 1 (LZTFL1)

Leucine Zipper Transcription Factor Like 1 (LZTFL1), also known as BBS17, encodes a ubiquitously expressed protein that localizes to the cytoplasm. The protein interacts with Bardet-Biedl Syndrome (BBS) proteins and, through its interaction with BBS protein complexes, regulates protein trafficking to the ciliary membrane. LZTFL1 regulates

ciliary localization of the BBSome complex and, together with the BBSome complex, controls SMO ciliary trafficking and contributes to the sonic hedgehog (SHH) pathway regulation.

- Nonsense mutations in this gene are associated with a form of Bardet-Biedl Syndrome. (See, e.g., Deffert et al. Am. J. Med. Genet. A. 143A(2):208-213 (2007)).
- LZTFL1 may also function as a tumor suppressor; possibly by interacting with E-cadherin and the actin cytoskeleton and thereby regulating the transition of epithelial cells to mesenchymal cells. Alternative splicing of LZTFL1 results in multiple transcript variants.

- The human LZTFL1 gene sequence is provided in GenBank Accession No. NG_033917.1, incorporated herein by reference. An exemplary human LZTFL1 nucleic acid sequence is provided in GenBank Accession No. NM_020347.4, incorporated herein by reference. An exemplary amino acid sequence of human LZTFL1 is provided by Q9NQ48-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the LZTFL1 gene.

15 *MKS Transition Zone Complex Subunit 1 (MKS1)*

- MKS Transition Zone Complex Subunit 1 (MKS1), also known as BBS13, is a component of the tectonic-like complex, a complex localized at the transition zone of primary cilia and acting as a barrier that prevents diffusion of transmembrane proteins between the cilia and plasma membranes. MKS1 localizes to the basal body and is involved in centrosome migration to the apical cell surface during early ciliogenesis, is required for formation of the primary cilium in ciliated epithelial cells, and is required for ciliary structure and function, including a role in regulating length and appropriate number through modulating centrosome duplication. MKS1 is also required for cell branching morphology.

- Mutations in this gene result in Meckel syndrome type 1 and in Bardet-Biedl syndrome type 13. (See, e.g., Xing et al. PLoS One 9(3):e90599 (2014)). Multiple transcript variants encoding different isoforms have been identified for this gene.

- The human MKS1 gene sequence is provided in GenBank Accession No. NG_013032.1, incorporated herein by reference. An exemplary human MKS1 nucleic acid sequence is provided in GenBank Accession No. NM_017777.4, incorporated herein by reference. An exemplary amino acid sequence of human MKS1 is provided by Q9NXB0-1,

incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the MKS1 gene.

Tripartite Motif Containing 32 (TRIM32)

Tripartite Motif Containing 32 (TRIM32), also known as BBS11, is a member of the tripartite motif (TRIM) family. The protein encoded by the TRIM32 gene contains three zinc-binding domains, a RING, a B-box type 1 and a B-box type 2, and a coiled-coil region. The protein encoded by TRIM32 localizes to cytoplasmic bodies and to the nucleus, where it interacts with the activation domain of the HIV-1 Tat protein. The TRIM32 protein also has E3 ubiquitin ligase activity and has been shown to ubiquitinate DTNBP1 (dysbindin) and promotes its degradation. It may also ubiquitinate BBS2.

Mutations in TRIM32 have been associated with muscular dystrophy, limb-girdle, autosomal recessive 8, and Bardet-Biedl syndrome (*See, e.g., Chiang et al. Proc. Natl. Acad. Sci. U.S.A. 103(16):3287-92 (2006)*).

The human TRIM32 gene sequence is provided in GenBank Accession No. NG_011619.1, incorporated herein by reference. An exemplary human TRIM32 nucleic acid sequence is provided in GenBank Accession No. NM_012210.4, incorporated herein by reference. An exemplary amino acid sequence of human TRIM32 is provided by Q13049-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the TRIM32 gene.

WD Repeat Containing Planar Cell Polarity Effector (WDPCP)

WD Repeat Containing Planar Cell Polarity Effector (WDPCP), also known as BBS15, is a cytoplasmic WD40 repeat protein. WDPCP is proposed to act as a planar cell polarity protein, which plays a critical role in collective cell movement and ciliogenesis by mediating septin localization. Together with FUZ, WDPCP is proposed to function as core component of the CPLANE (ciliogenesis and planar polarity effectors) complex involved in the recruitment of peripheral IFT-A proteins to basal bodies.

Mutations in this gene are associated with Bardet-Biedl syndrome and may also play a role in Meckel-Gruber syndrome. (*See, e.g., Kim et al. Science 329(5997):1337-40 (2010)*). Alternative splicing results in multiple transcript variants.

The human WDPCP gene sequence is provided in GenBank Accession No. NG_028144.2, incorporated herein by reference. An exemplary human WDPCP nucleic acid sequence is provided in GenBank Accession No. NM_001042692.3, incorporated herein by reference. An exemplary amino acid sequence of human WDPCP is provided by O95876-1, 5 incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the WDPCP gene.

Ribosomal Protein S6 Kinase A3 (RPS6KA3)

Ribosomal Protein S6 Kinase A3 (RPS6KA3) is a member of the RSK (ribosomal S6 kinase) family of serine/threonine kinases that acts downstream of ERK (MAPK1/ERK2 and 10 MAPK3/ERK1) signaling and mediates mitogenic and stress-induced activation of the transcription factors CREB1, ETV1/ER81, and NR4A1/NUR77, regulates translation through RPS6 and EIF4B phosphorylation, and mediates cellular proliferation, survival, and differentiation by modulating mTOR signaling and repressing pro-apoptotic function of BAD and DAPK1. In fibroblasts, RPS6KA3 is required for EGF-stimulated phosphorylation of 15 CREB1 and histone H3 at 'Ser-10', which results in the subsequent transcriptional activation of several immediate-early genes. In response to mitogenic stimulation (EGF and PMA), RPS6KA3 phosphorylates and activates NR4A1/NUR77 and ETV1/ER81 transcription factors and the cofactor CREBBP. Upon insulin-derived signal, RPS6KA3 acts indirectly on the transcription regulation of several genes by phosphorylating GSK3B at 'Ser-9' and 20 inhibiting its activity. RPS6KA3 also phosphorylates RPS6 in response to serum or EGF via an mTOR-independent mechanism and promotes translation initiation by facilitating assembly of the preinitiation complex. In response to insulin, RPS6KA3 phosphorylates EIF4B, enhancing EIF4B affinity for the EIF3 complex and stimulating cap-dependent translation. RPS6KA3 is involved in the mTOR nutrient-sensing pathway by directly 25 phosphorylating TSC2 at 'Ser-1798', which potently inhibits TSC2 ability to suppress mTOR signaling, and mediates phosphorylation of RPTOR, which regulates mTORC1 activity and may promote rapamycin-sensitive signaling independently of the PI3K/AKT pathway. RPS6KA3 mediates cell survival by phosphorylating the pro-apoptotic proteins BAD and DAPK1 and suppressing their pro-apoptotic function. RPS6KA3 promotes the survival of 30 hepatic stellate cells by phosphorylating CEBPB in response to the hepatotoxin carbon tetrachloride (CCl4). RPS6KA3 is also involved in cell cycle regulation by phosphorylating

the CDK inhibitor CDKN1B, which promotes CDKN1B association with 14-3-3 proteins and prevents its translocation to the nucleus and inhibition of G1 progression. In LPS-stimulated dendritic cells, RPS6KA3 is involved in TLR4-induced macropinocytosis, and in myeloma cells, it acts as effector of FGFR3-mediated transformation signaling, after direct

- 5 phosphorylation at Tyr-529 by FGFR3. RPS6KA3 negatively regulates EGF-induced MAPK1/3 phosphorylation via phosphorylation of SOS1. RPS6KA3 phosphorylates SOS1 at 'Ser-1134' and 'Ser-1161' that create YWHAB and YWHAЕ binding sites and which contribute to the negative regulation of MAPK1/3 phosphorylation and phosphorylates EPHA2 at 'Ser-897', the RPS6KA-EPHA2 signaling pathway controls cell migration.

- 10 Mutations in this gene have been associated with Coffin-Lowry syndrome (CLS), a rare X-linked semi-dominant syndrome characterized by severe psychomotor retardation, facial dysmorphism, digit abnormalities, and progressive skeletal deformations. (See, e.g., Delaunoy et al. Clin. Genet. 70(2): 161-6 (2006)).

The human RPS6KA3 gene sequence is provided in GenBank Accession No.

- 15 NG_007488.1, incorporated herein by reference. An exemplary human RPS6KA3 nucleic acid sequence is provided in GenBank Accession No. NM_004586.3, incorporated herein by reference. An exemplary amino acid sequence of human RPS6KA3 is provided by P51812-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the RPS6KA3 gene.

- 20 *5-Hydroxytryptamine Receptor 2C (HTR2C)*

5-Hydroxytryptamine Receptor 2C (HTR2C) is a seven-transmembrane G-protein-coupled receptor for 5-hydroxytryptamine (serotonin). HTR2C also functions as a receptor for various drugs and psychoactive substances, including ergot alkaloid derivatives, 1-2,5,-dimethoxy-4-iodophenyl-2-aminopropane (DOI) and lysergic acid diethylamide (LSD).

- 25 Ligand binding causes a conformational change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and modulates the activity of down-stream effectors. Beta-arrestin family members inhibit signaling via G proteins and mediate activation of alternative signaling pathways. Signaling activates a phosphatidylinositol-calcium second messenger system that modulates the activity of phosphatidylinositol 3-kinase and down-stream signaling cascades and promotes the release of Ca^{2+} ions from intracellular stores.
- 30 HTR2C also regulates neuronal activity via the activation of short transient receptor potential

calcium channels in the brain, and thereby modulates the activation of pro-opiomelanocortin neurons and the release of CRH that then regulates the release of corticosterone. HTR2C plays a role in the regulation of appetite and eating behavior, responses to anxiogenic stimuli and stress, and also plays a role in insulin sensitivity and glucose homeostasis.

5 The mRNA of HTR2C is subject to multiple RNA editing events, where adenosine residues encoded by the genome are converted to inosines. RNA editing is predicted to alter the structure of the second intracellular loop, thereby generating alternate protein forms with decreased ability to interact with G proteins. Abnormalities in RNA editing of HTR2C have been detected in victims of suicide that suffer from depression. In addition, naturally
10 occurring variation in the promoter and 5' non-coding and coding regions of HTR2C may show statistically significant association with mental illness and behavioral disorders. Alternative splicing results in multiple different transcript variants. Mutations in HTR2C have been linked to hyperphagia, hyperactivity, and obesity. (*See, e.g., Xu et al. Neuron. 60(4):582-9 (2008).*)

15 The human HTR2C gene sequence is provided in GenBank Accession No. NG_012082.2, incorporated herein by reference. An exemplary human HTR2C nucleic acid sequence is provided in GenBank Accession No. NM_001256760.2, incorporated herein by reference. An exemplary amino acid sequence of human HTR2C is provided by P28335-1, incorporated herein by reference. In an embodiment, the subject does not have or is not
20 identified as having a genetic mutation or genetic defect in the HTR2C gene.

Kinase Suppressor of Ras 2 (KSR2)

Kinase Suppressor of Ras 2 (KSR2) is an intracellular scaffolding protein involved in multiple signaling pathways. In particular, KSR2 is a location-regulated scaffold connecting MEK to RAF. KSR2 has been shown to have very low protein kinase activity and can
25 phosphorylate MAP2K1 at several Ser and Thr residues with very low efficiency *in vitro*. KSR2 acts as MAP2K1/MEK1-dependent allosteric activator of BRAF; upon binding to MAP2K1/MEK1, KSR2 dimerizes with BRAF and promotes BRAF-mediated phosphorylation of MAP2K1/MEK1 (*See, e.g., Lavoie et al. Nature 554:549-553(2018).*). Interaction with BRAF enhances KSR2-mediated phosphorylation of MAP2K1 *in vitro*.
30 KSR2 blocks MAP3K8 kinase activity and MAP3K8-mediated signaling. KSR2 also acts as a

negative regulator of MAP3K3-mediated activation of ERK, JNK and NF-kappa-B pathways, inhibiting MAP3K3-mediated interleukin-8 production.

5 Mutations in KSR2 are linked to hyperphagia in childhood, low heart rate, reduced basal metabolic rate and severe insulin resistance, suggesting that KSR2 is an important regulator of energy intake, energy expenditure, and substrate utilization in humans. (See, e.g., Pearce et al. Cell. 155(4):765-77 (2013)).

The human KSR2 gene sequence is provided within GenBank Accession No. NC_000012.12, incorporated herein by reference. An exemplary human KSR2 nucleic acid sequence is provided in GenBank Accession No. NM_173598.6, incorporated herein by
10 reference. An exemplary amino acid sequence of human KSR2 is provided by Q6VAB6-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the KSR2 gene.

Prokineticin 2 (PROK2)

The prokineticin 2 (PROK2) gene encodes a protein expressed in the suprachiasmatic
15 nucleus (SCN) circadian clock that may function as the output component of the circadian clock. The secreted form of the encoded protein may also serve as a chemoattractant for neuronal precursor cells in the olfactory bulb. Proteins from other vertebrates which are similar to the PROK2 gene product were isolated based on homology to snake venom; secretions from frog skin and have been shown to have diverse functions.

20 Mutations in PROK2 are associated with hypogonadotropic hypogonadism 4 with or without anosmia and Kallmann syndrome. Multiple transcript variants encoding different isoforms have been found for this gene. (See, e.g., Dodé et al. PLoS Genet. 2(10):e175 (2006)).

The human PROK2 gene sequence is provided in GenBank Accession No.
25 NG_008275.1, incorporated herein by reference. An exemplary human PROK2 nucleic acid sequence is provided in GenBank Accession No. NM_001126128.2, incorporated herein by reference. An exemplary amino acid sequence of human PROK2 is provided by Q9HC23-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the PROK2 gene.

Ras-Related Protein Rab-23 (RAB23)

Ras-Related Protein Rab-23 (RAB23) is a small GTPase of the Ras superfamily. The small GTPases Rab are involved in the regulation of diverse cellular functions associated with intracellular membrane trafficking, including autophagy and immune response to bacterial infection. Rabs cycle between an inactive GDP-bound form and an active GTP-bound form that is able to recruit to membranes different set of downstream effectors directly responsible for vesicle formation, movement, tethering, and fusion. Together with SUFU, the protein encoded by RAB23 prevents nuclear import of GLI1, and thereby inhibits GLI1 transcription factor activity. RAB23 also regulates GLI1 in differentiating chondrocytes, regulates GLI3 proteolytic processing, and modulates GLI2 and GLI3 transcription factor activity. RAB23 also plays a role in autophagic vacuole assembly, and mediates defense against pathogens, such as *S.aureus*, by promoting their capture by autophagosomes that then merge with lysosomes. RAB23 may play a role in central nervous system development by antagonizing sonic hedgehog signaling.

Mutations in RAB23 have been associated with cancer and Carpenter syndrome, a pleiotropic disorder with autosomal recessive inheritance, the cardinal features of which include craniosynostosis, polysyndactyly, obesity, and cardiac defects. (See, e.g., Jenkins et al. Am. J. Hum. Genet. 80(6):1162-70 (2007)). Alternative splicing results in multiple transcript variants.

The human RAB23 gene sequence is provided in GenBank Accession No. NG_012170.1, incorporated herein by reference. An exemplary human RAB23 nucleic acid sequence is provided in GenBank Accession No. NM_016277.5, incorporated herein by reference. An exemplary amino acid sequence of human RAB23 is provided by Q9ULC3-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the RAB23 gene.

Melanocortin 2 Receptor Accessory Protein 2 (MRAP2)

Melanocortin 2 Receptor Accessory Protein 2 (MRAP2) is a G-protein-coupled receptor accessory protein that modulates melanocortin receptor signaling and is involved in energy homeostasis. The encoded protein has been shown to interact with all known melanocortin receptors and may regulate both receptor trafficking and activation in response to ligands. MRAP2 is thought to play a central role in the control of energy homeostasis and

body weight regulation by increasing ligand-sensitivity of MC4R and MC4R-mediated generation of cAMP. MRAP2 may also act as a negative regulator of MC2R (e.g., by competing with MRAP for binding to MC2R and impairs the binding of corticotropin (ACTH) to MC2R). MRAP2 may also regulate activity of other melanocortin receptors (MC1R, MC3R and MC5R). MRAP2 has been implicated in energy control in rodents, notably via the melanocortin-4 receptor.

Deficiencies in MRAP2 have been associated with obesity (e.g., monogenic hyperphagic obesity, hyperglycemia, and hypertension) in both children and adults. (See, e.g., Baron et al. Nat. Med. 25(11):1733-1738 (2019)).

- 10 The human MRAP2 gene sequence is provided in GenBank Accession No. NG_051944.1, incorporated herein by reference. An exemplary human MRAP2 nucleic acid sequence is provided in GenBank Accession No. NM_138409.4, incorporated herein by reference. An exemplary amino acid sequence of human MRAP2 is provided by Q96G30-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the MRAP2 gene.
- 15

AF4/FMR2 Family Member 4 (AFF4)

AF4/FMR2 family member 4 (AFF4) is a component of the positive transcription elongation factor b (P-TEFb) complex, a core component of the super elongation complex (SEC), which is required to increase the catalytic rate of RNA polymerase II transcription by suppressing transient pausing by the polymerase at multiple sites along the DNA. In the SEC complex, AFF4 acts as a central scaffold that recruits other factors through direct interactions with ELL proteins (e.g., ELL, ELL2, or ELL3) and the P-TEFb complex. In case of infection by HIV-1 virus, the SEC complex is recruited by the viral Tat protein to stimulate viral gene expression.

- 25 Chromosomal aberrations involving ATF4 have been found in acute lymphoblastic leukemia (ALL). Missense mutations in AFF4 have been associated with CHOPS syndrome (C for cognitive impairment and coarse facies, H for heart defects, O for obesity, P for pulmonary involvement and S for short stature and skeletal dysplasia). (See, e.g., Izumi et al. Nat. Genet. 47(4):338-44 (2015)).

- 30 The human AFF4 gene sequence is provided in GenBank Accession No. NG_030340.1, incorporated herein by reference. An exemplary human AFF4 nucleic acid

sequence is provided in GenBank Accession No. NM_014423.4, incorporated herein by reference. An exemplary amino acid sequence of human AFF4 is provided by Q9UHB7-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the AFF4 gene.

5 *Adenylate Cyclase 3 (ADCY3)*

Adenylate cyclase 3 (ADCY3) is a membrane-associated enzyme and catalyzes the formation of the secondary messenger cyclic adenosine monophosphate (cAMP). ADCY3 catalyzes the formation of the signaling molecule cAMP in response to G-protein signaling and participates in signaling cascades triggered by odorant receptors via its function in cAMP biosynthesis. ADCY3 is required for the perception of odorants, for normal sperm motility, and normal male fertility. ADCY3 also plays a role in regulating insulin levels and body fat accumulation in response to a high fat diet. ADCY3 is widely expressed in various human tissues and may be involved in a number of physiological and pathophysiological metabolic processes. Two transcript variants encoding different isoforms have been identified for ADCY3.

Loss of function mutations in ADCY4 have been associated with monogenic severe obesity. (See, e.g., Saeed et al. Nat. Genet. 50(2):175-179 (2018)).

The human ADCY3 gene sequence is provided within GenBank Accession No. NC_000002.12, incorporated herein by reference. An exemplary human ADCY3 nucleic acid sequence is provided in GenBank Accession No. NM_001320613.2, incorporated herein by reference. An exemplary amino acid sequence of human ADCY3 is provided by O60266-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the ADCY3 gene.

TUB Bipartite Transcription Factor (TUB)

25 TUB Bipartite Transcription Factor (TUB) is a member of the Tubby family of bipartite transcription factors that functions in signal transduction from heterotrimeric G protein-coupled receptors. The crystal structure has been determined for a similar protein in mouse, which functions as a membrane-bound transcription regulator that translocates to the nucleus in response to phosphoinositide hydrolysis. TUB binds to membranes containing phosphatidylinositol 4,5-bisphosphate and has been shown to bind DNA *in vitro*. TUB may

contribute to the regulation of transcription in the nucleus and could be involved in the hypothalamic regulation of body weight. TUB contributes to stimulation of phagocytosis of apoptotic retinal pigment epithelium (RPE) cells and macrophages. Two transcript variants encoding distinct isoforms have been identified for this gene.

- 5 Mutations in TUB have been associated with obesity and retinal dystrophy (e.g., characterized by obesity, night blindness, decreased visual acuity, and electrophysiological features of a rod cone dystrophy). (*See, e.g., Borman et al. Hum. Mutat. 35(3):289-93 (2014).*)

The human TUB gene sequence is provided in GenBank Accession No.

- 10 NG_029912.1, incorporated herein by reference. An exemplary human TUB nucleic acid sequence is provided in GenBank Accession No. NM_003320.4, incorporated herein by reference. An exemplary amino acid sequence of human TUB is provided by P50607-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the TUB gene.

- 15 *Orthopedia Homeobox (OTP)*

Orthopedia Homeobox (OTP) is a member of the homeodomain (HD) family. HD family proteins are helix-turn-helix transcription factors that play key roles in the specification of cell fates. OTP may function during brain development, specifically in the differentiation of hypothalamic neuroendocrine cells. OTP is also believed to be involved in
20 mammalian energy homeostasis and behavior.

Disruption of OTP has been associated with obesity, marasmus, Kwashiorkor, and anxiety (*See, e.g., Moir et al. Mol. Metab. 6(11):1419-1428 (2017).*)

The human OTP gene sequence is provided within GenBank Accession No.

- 25 NC_000005.10, incorporated herein by reference. An exemplary human OTP nucleic acid sequence is provided in GenBank Accession No. NM_032109.3, incorporated herein by reference. An exemplary amino acid sequence of human OTP is provided by Q5XKR4-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the OTP gene.

G-Protein Coupled Receptor 101 (GPR101)

G-Protein Coupled Receptor 101 (GPR101) is an orphan G protein-coupled receptor of largely unknown function. The encoded protein is a member of a family of proteins that contain seven transmembrane domains and transduce extracellular signals through heterotrimeric G proteins.

Diseases associated with GPR101 include Pituitary Adenoma 2, Growth Hormone-Secreting and Chromosome Xq26.3 Duplication Syndrome. Neuronal GLP1Rs has been shown to mediate body weight and anorectic effects of liraglutide but are not required for glucose-lowering effects. (See, e.g., Sisley et al. J. Clin. Invest. 124(6):2456-63 (2014)).

The human GPR101 gene sequence is provided in GenBank Accession No. NG_016367.1, incorporated herein by reference. An exemplary human GPR101 nucleic acid sequence is provided in GenBank Accession No. NM_054021.2, incorporated herein by reference. An exemplary amino acid sequence of human GPR101 is provided by Q96P66-1, incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the GPR101 gene.

T-Box Transcription Factor 3 (TBX3)

T-Box Transcription Factor 3 (TBX3) is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box. T-box genes encode transcription factors involved in the regulation of developmental processes. TBX3 is a transcriptional repressor and is thought to play a role in the anterior/posterior axis of the tetrapod forelimb. TBX3 acts as a negative regulator of PML function in cellular senescence. TBX3 may also play a role in limb pattern formation. Alternative splicing of this gene results in three transcript variants encoding different isoforms.

Mutations that disrupt the DNA-binding domain of TBX3 have been associated with Ulnar-mammary syndrome (UMS), a pleiotropic disorder affecting limb, apocrine-gland, tooth, hair, and genital development. (See, e.g., Bamshad et al. Am. J. Hum. Genet. 64(6):1550-62 (1999)).

The human TBX3 gene sequence is provided in GenBank Accession No. NG_008315.1, incorporated herein by reference. An exemplary human TBX3 nucleic acid sequence is provided in GenBank Accession No. NM_016569.4, incorporated herein by reference. An exemplary amino acid sequence of human TBX3 is provided by O15119-1,

incorporated herein by reference. In an embodiment, the subject does not have or is not identified as having a genetic mutation or genetic defect in the TBX3 gene.

In embodiments of any method described herein, the method comprises treating a subject having a mutation in a gene listed in Table 2 below. In
 5 embodiments, a method described herein comprises use of a MC4R agonist described herein to treat a subject a non-genetic obesity, e.g., a subject that does not have a mutation in an MC4R pathway agonizable gene, e.g., as listed in Table 2. In
 10 embodiments, a method described herein comprises use of a MC4R agonist described herein to treat a subject having a mutation in an MC4R pathway agonizable gene, e.g., as listed in Table 2. Table 2 describes exemplary genes, alleles, transcripts, and proteins, though other genes, alleles, transcripts, and proteins may be included.

Table 2: Exemplary MC4R pathway agonizable genes, alleles, and transcripts

Gene Name	NCBI Reference (exemplary transcripts)	UniProt Reference (Amino Acid)
ARL6	NM_001278293.3	Q9H0F7
RAI1	NM_030665.4	Q7Z5J4-1
SRC1	NM_003743.5	Q15788-1
BBS19	NM_001177701.3	Q9BW83-1
BBS21	NM_177965.4	Q96NL8-1
CEP290	NM_025114.4	O15078-1
IFT74	NM_001099222.2	Q96LB3-1
LZTFL1	NM_020347.4	Q9NQ48-1
MKS1	NM_017777.4	Q9NXB0-1
TRIM32	NM_012210.4	Q13049-1
WDPCP	NM_001042692.3	O95876-1
RPS6KA3	NM_004586.3	P51812-1
HTR2C	NM_001256760.2	P28335-1
KSR2	NM_173598.6	Q6VAB6-1
PROK2	NM_001126128.2	Q9HC23-1

RAB23	NM_016277.5	Q9ULC3-1
MRAP2	NM_138409.4	Q96G30-1
AFF4	NM_014423.4	Q9UHB7-1
ADCY3	NM_001320613.2	O60266-1
TUB	NM_003320.4	P50607-1
OTP	NM_032109.3	Q5XKR4-1
GPR101	NM_054021.2	Q96P66-1
TBX3	NM_016569.4	O15119-1

Additional MC4R pathway agonizable genes

Additional MC4R pathway agonizable genes useful in the methods disclosed herein are described as follows:

- 5 Acyl-CoA Binding Domain Containing 7 (ACBD7), also known as BA455B2.2, has been associated with food intake, energy expenditure, and body weight in preclinical models. (See, e.g., Lanfray et al. Elife. 15;5:e11742 (2016)).

Agouti Related Neuropeptide (AGRP), also known as ASIP2, has been associated with hyperphagia and obesity. (See, e.g., Carroll et al. Clin. Dermatol. 22(4):345-9 (2004)).

- 10 Cell Adhesion Molecule 1 (CADM1), also known as TSLC1 or IGSF4, has been associated with obesity. (See, e.g., Rathjen et al. Nat. Neurosci. 20(8):1096-1103 (2017)).

Cell Adhesion Molecule 2 (CADM2), also known as IGSF4D, has been associated with obesity. (See e.g., Li et al. Hum. Genet. 132(7):793-801 (2013)).

- 15 Cocaine and Amphetamine-Regulated Transcript Protein (CARTPT), also known as CART, has been associated with obesity. (See, e.g., Asnicar et al. Endocrinology. 42(10):4394-400 (2001)).

Coiled-Coil Domain Containing 28B (CCDC28B) has been associated with Bardet-Biedl syndrome. (See, e.g., Novas et al. Sic. Rep. 14;8(1):3019 (2018)).

- 20 Cholecystokinin (CCK), also known as Prepro-Cholecystokinin, has been associated with obesity and body mass index. (See, e.g., Namjou et al. Front. Genet. 3;4:268 (2013)).

Cannabinoid Receptor 1 (CNR1), also known as CNR, has been associated with obesity and body fat mass and distribution. (See, e.g., Russo et al. J. Endocrinol. Metab. 92(6):2382-6 (2007)).

CREB Binding Protein (CREBBP), also known as RSTS, has been associated with Rubinstein-Taybi syndrome. (*See, e.g.,* Stevens et al. Am. J. Med. Genet. A. 155A(7):1680-4 (2011)).

5 CREB3 Regulatory Factor (CREBRF), also known as C5orf41, has been associated with obesity and diabetes. (*See, e.g.,* Hanson et al. Diabetologia. 62(9):1647-1652 (2019)).

Cullin 4B (CUL4B), also known as KIAA0695, MRXHF2, MRXS15, MRXSC, and SFM2, has been associated with mental retardation, X-linked, syndromic 15 (Cabezas type). (*See, e.g.,* Tarpey et al. Am. J. Hum. Genet. 80(2):345-10 52 (2007)).

DNA Methyltransferase 3 Alpha (DNMT3A), also known as HESJAS and TBR5, encodes a protein involved in de novo methylation. (*See, e.g.,* Xie S. et al. Gene 236(1):87-95 (1999)).

Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1B (DYRK1B), 15 also known as Minibrain-related kinase, has been associated with abdominal obesity-metabolic syndrome 3. (*See, e.g.,* Keramati et al. N. Engl. J. Med. 370(20):1909-1919 (2014)).

Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1), also known as NPP5, M6S1, and PDNP1, has been associated with obesity. (*See, e.g.,* Valli-Jaakola 20 et al. Obesity. 16(9):2113-9 (2008)).

E1A Binding Protein P300 (EP300), also known as Histone Acetyltransferase P300, has been associated with Rubinstein-Taybi syndrome. (*See, e.g.,* Stevens et al. Am. J. Med. Genet. A. 155A(7):1680-4 (2011)).

FMRP Translational Regulator 1 (FMR1), also known as POF1 and POF, has 25 been associated with Fragile X Syndrome. (*See, e.g.,* Raspa et al. Am. J. Intellect. Dev. Disabil. 115(6):482-95 (2010)).

FTO Alpha-Ketoglutarate Dependent Dioxygenase (FTO), also known as FTO Alpha-Ketoglutarate Dependent Dioxygenase, has been associated with obesity-related traits including body mass index, hip circumference, and weight. (*See e.g.,* 30 Scuteri et al. PLoS. Genet. 3(7):e115 (2007)).

Ghrelin and Obestatin Prepropeptide (GHRL), also known as Prepro-Appetite Regulatory Hormone, has been associated with obesity. (*See, e.g.*, J. Clin. Endocrinol. Metab. 87(8):4005-8 (2002)).

5 Gastric Inhibitory Polypeptide Receptor (GIPR), also known as GIP-R and PGQTL2, has been associated with body mass index and energy intake and expenditure pathways in obesity. (*See, e.g.*, Turcot et al. Nat. Genet. 50(1):26-41 (2018)).

Glucagon Like Peptide 1 Receptor (GLP1R), also known as GLP-1, has been associated with food intake and body weight regulation. (*See, e.g.*, Sisley et al. J. Clin. Invest. 124(6):2456-63 (2014)).

10 Inositol Polyphosphate-5-Phosphatase E (INPP5E), also known as JBTS1, has been associated with Joubert syndrome and MORM syndrome, an autosomal recessive congenital disorder characterized by mental retardation, truncal obesity, retinal dystrophy, and micropenis. (*See, e.g.*, Jacoby et al. Nat. Genet. 41(9):1027-31 (2009)).

15 Insulin (INS), also known as IDDM2 and IDDM1, has been associated with body mass index and obesity. (*See, e.g.*, Antúñez-Ortiz et al. Biomed. Res. Int. 2017:2432957 (2017)).

Insulin Induced Gene 2 (INSIG2), also known as Insulin Induced Protein 2, has been associated with feedback control of lipid synthesis and obesity in children. (*See, e.g.*, Kaulfers et al. PLoS One 10(1):e0116340 (2015)).

20 Insulin Receptor Substrate 1 (IRS1), also known as HIRS-1, has been associated with obesity, type II diabetes, and susceptibility to insulin resistance. (*See, e.g.*, Clausen et al. Lancet. 346(8972):397-402 (1995)).

25 Insulin Receptor Substrate 4 (IRS4), also known as Pp160, CHNG9, PY160, and Py160, has been associated with obesity, hyperglycemia, and insulin resistance. (*See, e.g.*, Sadagurski et al. Mol. Metab. 23;3(1):55-63 (2013)).

Insulin Gene Enhancer Protein (ISL1), also known as Islet-1 and Isl-1, is a member of the LIM/homeodomain family of transcription factors, and mutations in this gene have been associated with, inter alia, maturity-onset diabetes. (*See, e.g.*, Tanizawa Y et al. Diabetes (1994)).

30 Methyl-CpG Binding Protein 2 (MeCP2), also known as AUTSX3, MRXS13, MRX16, RTS, and RTT, encodes a nuclear protein related to onset of Rett syndrome, a

progressive neurologic developmental disorder. Amir, R.E. et al. *Nat Genet* 23(2):185-8 (1999)

Neuropilin 1 (NRP1), also known as CD304 and BDCA4, encodes one of two neuropilins involved in signaling pathways that control cell migration. NRP1 is associated with cerebral arteriopathy, autosomal dominant, and neuroma. (See, e.g., Soker, S. et al *Cell* 92(6):735-745).

Neuropilin 2 (NRP2), also known as NPN2, NP2, and PRO2714, may play a role in cardiovascular development, axon guidance, and tumorigenesis. (See, e.g., Chen, H. et al. *Neuron* 19(3):547-549 (1997)).

10 RPGRIP1L Like (RPGRIP1L), also known as FTM, PPP1R134, CORS3, MKS5, JBTS7, and KIAA1005, has been found to interact with neprocystin-4. Defects in this gene have been associated with Joubert syndrome type 7 and Meckel syndrome type 5 (Nagase, T et al *DNA Res* 6(1):63-70 (1999)).

Plexin A1 (PLXNA1), also known as NOV and PLXN1, is associated with hereditary congenital facial paresis and nephronophthisis 4. (See, e.g., Maestrini, E. et al. *Proc Natl Acad Sci USA* 93(2):674-678 (1996)).

Plexin A2 (PLXNA2), also known as OCT, KIAA0463, and FLJ11751, is a plexin-A family member believed to be related to signal transduction from semaphorin-3A and semaphorin-3B. (See, e.g., also Coric, V. et al. *Depress Anxiety* 20 27(5):417-425 (2010)).

Plexin A3 (PLXNA3), also known as XAP-6, is involved in cytoskeletal remodeling and apoptosis. This gene has been shown to be important in axon pathfinding in developing nervous systems and is associated with tumor progression. (See, e.g., Maestrini, L. et al. *Proc Natl Acad Sci USA* 93(2):674-678 (1996)).

25 Plexin A4 (PLXNA4), also known as FAYV2820, KIAA1550, and PRO34003, is associated with various signal transduction pathways, particularly involving semaphorin-3A and semaphorin-3B. (See, e.g., Imboden, M. *J Allergy Clin Immunol* 129(5):1218-1228 (2012)).

Potassium Channel Tetramerization Domain Containing 15 (KCTD15), also known as BTB/POZ Domain-Containing Protein KCTD15, has been associated with

body mass index and obesity in children. (*See, e.g., Zhao et al. Obesity 17(12):2254-7 (2009)*).

Kinase D Interacting Substrate 220 (KIDINS220), also known as ARMS, KIAA1250, and SINO, has been associated with spastic paraplegia, intellectual disability, nystagmus, and obesity. (*See, e.g., Josifova et al. Hum. Mol. Genet. 25(11):2158-2167 (2016)*).

Melanin Concentrating Hormone Receptor 1 (MCHR1), also known as GPR24, has been associated with regulation of food intake and body weight. (*See, e.g., Marsh et al. Proc. Natl. Acad. Sci. U.S.A. 99(5):3240-5 (2002)*).

Methionine Sulfoxide Reductase A (MSRA), also known as PMSR, has been associated with several obesity-related traits in children. (*See, e.g., Albuquerque et al. J. Hum. Genet. 59(6):307-13 (2014)*).

Necdin, MAGE Family Member (NDN), also known as PWCR, has been associated with Prader-Willi syndrome. (*See, e.g., Jay et al. Nat. Genet. 17(3):357-61 (1997)*).

Neuronal Growth Regulator 1 (NEGR1), also known as Neurotractin, IGLON4, DMML2433, KILON, and Ntra, has been associated with body mass index. (*See, e.g., Zhao et al. Obesity. 17(12):2254-7 (2009)*).

Neurexin 2 (NLGN2), also known as KIAA1366, has been associated with anxiety, autism, intellectual disability, hyperphagia, and obesity. (*See, e.g., Am. J. Med. Genet. A. 173(1):213-216 (2017)*).

Neuropeptide Y (NPY), also known as PYY4, has been associated with obesity. (*See, e.g., van Rossum et al. Int. J. Obes. 30(10):1522-8 (2006)*).

Nuclear Receptor Subfamily 0 Group B Member 2 (NR0B2), also known as SHP1, has been associated with mild and early-onset obesity. (*See, e.g., Nishigori et al. PNAS. 98(2):575-80 (2001)*).

Neurotrophic Receptor Tyrosine Kinase 2 (NTRK2), also known as Trk-B, has been associated with severe obesity and developmental delay (e.g., NTRK2 deficiency obesity). (*See, e.g., Yeo et al. Nat. Neurosci. 7(11):1187-9 (2004)*).

Opioid Receptor Mu 1 (OPRM1), also known as MOR1, MOP, LMOR, OPRM, and HMOP, has been associated with associated with metabolism and the MC4R pathway (*See, e.g., Olszewski et al. Neuroreport 12(8):1727-1730 (2001)*).

Pericentrin (PCNT), also known as Kendrin and PCNT2, has been associated with Majewski osteodysplastic primordial dwarfism type II. (*See, e.g.,* Rauch et al. Science. 8;319(5864):816-9 (20008)).

5 Pleckstrin Homology Domain Interacting Protein (PHIP), also known as WDR11, Ndrp, DCAF14, BRWD2. (*See, e.g.,* Webster et al. Cold Spring Harb Mol Case Stud 2(6):a001172 (2016)).

Proprotein Convertase Subtilisin/Kexin Type 2 (PCSK2), also known as NEC2, has been associated with glucose homeostasis, food intake, ultimately body mass. (*See, e.g.,* Anini et al. Int. J. Obes. 34(11):1599-607 (2010)).

10 PHD Finger Protein 6 (PHF6), also known as BFLS and BORJ, has been associated with Börjeson-Forssman-Lehman syndrome, a syndrome characterized by moderate to severe mental retardation, epilepsy, hypogonadism, hypometabolism, obesity with marked gynecomastia, swelling of subcutaneous tissue of the face, narrow palpebral fissure, and large but not deformed ears. (*See, e.g.,* Lower et al. 15 Nat. Genet. 32(4):661-5 (2002)).

Pro-Melanin Concentrating Hormone (PMCH), also known as MCH and PpMCH, has been associated with regulation of food intake and body weight. (*See, e.g.,* Shimada et al. Nature. 396(6712):670-4 (1998)).

Peroxisome Proliferator Activated Receptor Gamma (PPARG), also known as 20 NR1C3, PPARG1, PPARG2, CMT1, and GLM1, has been associated with obesity in children and adolescents. (*See, e.g.,* Ochoa et al. Int. J. Obes. Relat. Metab. Disord. 28 Suppl 3:S37-41 (2004)).

Peptide YY (PYY), also known as Peptide Tyrosine Tyrosine, has been associated with regulation of food intake and obesity. (*See, e.g.,* Ahituv et al. Hum. 25 Mol. Genet. 1;15(3):387-91 (2006)).

Syndecan 3 (SDC3), also known as SDCN, has been associated with energy balance, obesity, body mass index, and LDL cholesterol. (*See, e.g.,* Chang et al. Int. J. Endocrinol. 30;2018:9282598 (2018)).

30 SEC16 Homolog B, Endoplasmic Reticulum Export Factor (SEC16B), also known as LZTR2, has been associated with body mass index. (*See, e.g.,* Felix et al. Hum. Mol. Genet. 15;25(2):389-403 (2016)).

Solute Carrier Family 6 Member 14 (SLC6A14), also known as BMIQ11, has been associated with body mass index and obesity. (*See, e.g.,* Suviolahti et al. J. Clin. Invest. 112(11):1762-72 (2003)).

5 Small Nuclear Ribonucleoprotein Polypeptide N (SNRPN), also known as PWCR, has been associated with Prader-Willi Syndrome. (*See, e.g.,* Kuslich et al. Am. J. Hum. Genet. 64(1):70-6 (1999)).

Thyroid Hormone Receptor Beta (THRB), also known as ERBA2 and PRTH, has been associated with regulation of food intake and body weight. (*See e.g.,* Amorim et al. J. Endocrinol. 203(2):291-9 (2009)).

10 Transient Receptor Potential Cation Channel Subfamily C Member 5 (TRPC5), also known as PPP1R159, TRP-5, HTRP5. (see, e.g., Sossey-Alaoui, K et al. Genomics 60(3):330-3340 (1999)).

Transmembrane Protein 18 (TMEM18), also known as LncND, has been associated with body mass index and body weight regulation. (*See, e.g.,* Willer et al. Nat. Genet. 15 41(1):25-34 (2009)).

Transmembrane Protein 67 (TMEM67), also known as MKS3, has been associated with Bardet-Biedl Syndrome. (*See, e.g.,* Leitch et al. Nat. Genet. 40(4):443-8 (2008)).

Trafficking Protein Particle Complex 9 (TRAPPC9), also known as NIBP, has been associated with mental retardation, autosomal recessive 13. (*See, e.g.,* Marangi et al. Eur. J. 20 Hum. Genet. 21(2):229-32 (2013)).

Uncoupling Protein 1 (UCP1), also known as thermogenin, SLC25A7, and UCP, has been associated with obesity. (*See, e.g.,* Ramos et al. BMC Med. Genet. 7;13:101 (2012)).

Uncoupling Protein 3 (UCP3), also known as SLC25A9, has been associated with metabolic fuel partitioning and obesity. (*See, e.g.,* Argyropoulos et al. J. Clin. Invest. 25 1;102(7):1345-51 (1998)).

Vacuolar Protein Sorting 13 Homolog B (VPS13B), also known as CHS1 and COH1, has been associated with Cohen syndrome, an autosomal recessive disorder with variability in the clinical manifestations, characterized by mental retardation, postnatal microcephaly, facial dysmorphism, pigmentary retinopathy, myopia, and intermittent neutropenia. (*See, e.g.,* Seifert et al. J. Med. Genet. 43(5):e22 (2006)). 30

In an embodiment, the MC4R pathway agonizable gene comprises POMC, PCSK1, LEPR, LEP, SDCCAG8, SH2B1, CPE, ALMS1, BBS1, BBS2, BBS4, BBS5, BBS6, BBS7, BBS8, BBS9, BBS10, BBS12, BBS18, BBS20, GNAS, MC3R, NHLH2, SIM1, BDNF, NTRK2, MAGEL2, or a 16p11.2 deletion. In an
5 embodiment, the subject does not have a genetic mutation or genetic variant in a gene selected from POMC, PCSK1, LEPR, LEP, SDCCAG8, SH2B1, CPE, ALMS1, BBS1, BBS2, BBS4, BBS5, BBS6, BBS7, BBS8, BBS9, BBS10, BBS12, BBS18, BBS20, GNAS, MC3R, NHLH2, SIM1, BDNF, NTRK2, and MAGEL2, or a 16p11.2 deletion.

10

Obesity

The present disclosure features methods for treating a subject having obesity, e.g., a non-genetic obesity. In an embodiment, the obesity is hypothalamic obesity. In an embodiment, the obesity is due to a disease, disorder, or condition relating to an MC4R
15 pathway agonizable gene. In an embodiment, the disease, disorder, or condition is characterized by a mutation (e.g., a substitution mutation, a deletion mutation, or a polymorphism) in the MC4R pathway agonizable gene. In embodiments, the methods comprise administering to the subject an MC4R agonist or compositions described herein, e.g., a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX),
20 (X), (XI), or (XII), (e.g., as described herein) or a pharmaceutically acceptable salt thereof. In an embodiment, the MC4R agonist is setmelanotide (i.e., Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140))

Hypothalamic Obesity

25 Hypothalamic obesity (HO) is a form of obesity caused by physical or inherited damage to the hypothalamus, resulting in symptoms such as uncontrollable hunger, rapid and/or excessive weight gain, and a low metabolic rate. The hypothalamus is responsible for regulating energy balance and body weight by integrating metabolic information that governs the drive for food intake and energy expenditure, primarily via signaling through the MC4
30 receptor (MC4R), which has been identified as the critical melanocortin receptor involved in the regulation of body weight, hunger, and energy homeostasis (Holland 2019). Recently,

MRI findings in patients with HO displayed anatomical disruption of the hypothalamus which contains MC4 receptors and POMC neurons residing in the arcuate nuclei and in the paraventricular nucleus, respectively.

Damage to the arcuate nucleus, paraventricular nucleus, dorsomedial nucleus, and dorsal hypothalamic area most commonly results in impairments in regulation of both peripheral energy expenditure and satiety (Abuzzahab 2019). This impairment in the MC4R pathway may lead to a high degree of sudden, severe, and sustained weight gain which is unresponsive to general lifestyle changes or current anti-obesity pharmacotherapies (Sterkenburg 2015). Approximately 50% of patients with HO also manifest with a marked increase in hunger. A key difference from other disease entities which may originate due to impairment to the MC4 pathway is that in the case of HO, the impairment is due to structural damage, whereas in the other diseases it is due to a genetic impairment; several genetic variants have been associated with reduced signalling through the MC4 pathway, a reduction in α -MSH and consequent hyperphagia and obesity.

In addition to tumor (e.g., craniopharyngiomas, gliomas, pituitary adenomas, hamartomas), and/or the surgery or radiation therapy used to treat the tumor (Hochberg 2010), other much rarer causes of injury include inflammatory conditions involving the hypothalamus or trauma. Craniopharyngiomas represent the most common tumor associated with the development of HO and accounts for 5% to 15% of pediatric intracranial tumors (Muller 2022). A bimodal age distribution has been observed for new cases of craniopharyngioma with a first peak seen in children aged 4 to 14 years and a second peak in adults ages >40 years (Ostrom 2021).

Other causes for this condition include swelling in the brain, head trauma, brain surgery, or the presence of certain genetic mutations. Genetic mutations in the LEP, LEPR, POMC, MC4R, and CART genes may also lead to this disease (see, e.g., Kim et al. *Ann Pediatr Endocrinol Metab* (2013) 18(4): 161-167). Hypothalamic obesity has also been linked to diminished α -MSH levels (see, e.g., Roth et al. *Metabol Clin Exper* (2010) 59:186-194).

Hypothalamic obesity is a distinct disease that differs from general obesity (e.g., a genetic obesity or other non-genetic obesity or a syndromic disease). For example, HO is most often the result of an acquired injury as opposed to a genetically driven impairment in

the MC4R pathway which results in a decrease in the hormone α -MSH. In addition, a subject that has or is identified as having HO may exhibit a dramatic shift in clinical phenotype compared to a subject having general obesity (e.g., a genetic obesity or other non-genetic obesity or a syndromic disease), such as rapid weight gain,
5 increased hunger, and decreased energy dating from the time of the injury. Further, a subject that has or is identified as having HO often does not present with a secondary or additional disease manifestations that frequently characterizes some genetic obesities.

In an embodiment, the subject has obesity, e.g., hypothalamic obesity,
10 wherein the fasting peripheral α -MSH is between about 4 to about 10 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is between about 4 to about 9, 4 to about 8, 4 to about 7, 4 to about 6, or 4 to about 5 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is between about 4 to about 9 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g.,
20 hypothalamic obesity, wherein the fasting peripheral α -MSH is between about 4 to about 8 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is between about 4 to about 7 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is between about 4 to about 6 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is between about 4 to about 5 fmol/mL relative to the fasting
30 peripheral α -MSH is between about 4 to about 5 fmol/mL relative to the fasting

peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject.

In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 10 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 9, 8, 7, 6, 5 or 4 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 9 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 8 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 7 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 6 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 5 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 4 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject.

In an embodiment, the subject has obesity, e.g., hypothalamic obesity, wherein the fasting peripheral α -MSH is less than 4 fmol/mL relative to the fasting peripheral α -MSH of between about 15 to about 30 fmol/mL of a healthy non-obese subject.

In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to lifestyle modification (e.g., alterations in diet or exercise). In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to a modification in diet. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to caloric restriction. In an embodiment, the subject has obesity, e.g.,

hypothalamic obesity, that is unresponsive to a reduction in food intake. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to increased physical exercise, e.g., increased caloric expenditure achieved during exercise.

- 5 In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the absence of hyperphagia. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the absence of hyperphagia, wherein the daily most hunger score of the subject is statistically
- 10 equivalent, e.g., within the standard error of the measurement, to the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the absence of hyperphagia, wherein the weekly average of the daily most hunger score is subject is
- 15 statistically equivalent, e.g., within the standard error of the measurement, to the weekly average of the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. . In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the absence of hyperphagia, wherein the daily most hunger
- 20 score of the subject is not clinically meaningful, e.g., less than 2 points, relative to the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the absence of hyperphagia, wherein the weekly average of the daily most
- 25 hunger score is subject is not clinically meaningful, e.g., less than 2 points, relative to the weekly average of the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the absence of hyperphagia, wherein the change in the IWQOL
- 30 or IQWOL-Lite score of the subject is not clinically meaningful, relative to the

IWQOL or IQWOL-Lite score of the subject prior to the development of hypothalamic obesity in the subject.

- In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure in the presence of hyperphagia. In an
- 5 embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the presence of hyperphagia, wherein the increase in the daily most hunger score of the subject is clinically meaningful, e.g., greater than 2 points, relative to the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g.,
- 10 hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the presence of hyperphagia, wherein the increase in the weekly average of the daily most hunger score in the subject is clinically meaningful, e.g., greater than 2 points, relative to the weekly average of the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g.,
- 15 hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) in the presence of hyperphagia, wherein the decrease in the IWQOL or IQWOL-Lite score of the subject is clinically meaningful, relative to the IWQOL or IQWOL-Lite score of the subject prior to the development of hypothalamic obesity in the subject.

- In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized
- 20 by a decrease in resting energy expenditure and a reduction in physical activity in the absence of hyperphagia. . In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) and a reduction in physical activity in the absence of hyperphagia, wherein the daily most hunger score of the subject is statistically equivalent, e.g., within the standard error of the measurement, to the
- 25 daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) and a reduction in physical activity in the absence of hyperphagia, wherein the weekly average of the daily most hunger score is subject is statistically equivalent, e.g., within the standard error of the measurement,
- 30 to the weekly average of the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has

obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) and a reduction in physical activity in the absence of hyperphagia, wherein the daily most hunger score of the subject is not clinically meaningful, e.g., less than 2 points, relative to the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the
5 subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) and a reduction in physical activity in the absence of hyperphagia, wherein the weekly average of the daily most hunger score is subject is not clinically meaningful, e.g., less than 2 points, relative to the weekly average of the
10 daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) and a reduction in physical activity in the absence of hyperphagia, wherein the change in the IWQOL or IQWOL-Lite score of the subject is not clinically
15 meaningful, relative to the IWQOL or IQWOL-Lite score of the subject prior to the development of hypothalamic obesity in the subject.

In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure and a reduction in physical activity in the presence of hyperphagia. In an embodiment, the subject has obesity,
20 e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) and a reduction in physical activity in the presence of hyperphagia, wherein the increase in the daily most hunger score of the subject is clinically meaningful, e.g., greater than 2 points, relative to the daily most hunger score of the of the subject prior to the development of hypothalamic obesity in the subject. In an embodiment,
25 the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy expenditure (REE) and a reduction in physical activity in the presence of hyperphagia, wherein the increase in the weekly average of the daily most hunger score in the subject is clinically meaningful, e.g., greater than 2 points, relative to the weekly average of the daily most hunger score of the of the subject prior to the
30 development of hypothalamic obesity in the subject. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, characterized by a decrease in resting energy

expenditure (REE) and a decrease in physical activity in the presence of hyperphagia, wherein the decrease in the IWQOL or IQWOL-Lite score of the subject is clinically meaningful, relative to the IWQOL or IQWOL-Lite score of the subject prior to the development of hypothalamic obesity in the subject.

- 5 In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to bariatric surgery. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to a bariatric surgery procedure including gastric bypass, gastric band, gastric sleeve, duodenal switch, gastric balloon, and intestinal barrier, *inter alia*. . In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is
- 10 unresponsive to a gastric bypass procedure . In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to a gastric band procedure. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to a gastric sleeve procedure. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to a duodenal switch procedure. In an embodiment, the subject has obesity,
- 15 e.g., hypothalamic obesity, that is unresponsive to gastric balloon procedure. . In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to an intestinal barrier procedure.
- In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to pharmacologic therapy, e.g., therapy with sympathomimetic agents, somatostatin analogs,
- 20 analogs of glucagon-like peptide (GLP-1), metformin, a combination of metformin and fenofibrate, a combination metformin and diazoxide, central nervous system (CNS) stimulants, and melatonin. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to pharmacologic therapy comprising sympathomimetic agents.
- In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to
- 25 pharmacologic therapy comprising somatostatin analogs. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to pharmacologic therapy comprising analogs of glucagon-like peptide (GLP-1). In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to pharmacologic therapy comprising metformin. In an embodiment, the subject has obesity, e.g., hypothalamic
- 30 obesity, that is unresponsive to pharmacologic therapy comprising a combination of metformin and fenofibrate. In an embodiment, the subject has obesity, e.g., hypothalamic

obesity, that is unresponsive to pharmacologic therapy comprising a combination of metformin and diazoxide. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that is unresponsive to pharmacologic therapy comprising central nervous system (CNS) stimulants. In an embodiment, the subject has obesity, e.g., hypothalamic obesity, that
5 is unresponsive to pharmacologic therapy comprising melatonin.

Additional diseases, disorders, or conditions that may be treated by administration of an MC4R agonist or compositions described herein, e.g., a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), (e.g., as described herein) or a pharmaceutically acceptable salt
10 thereof include 5p3 microduplication syndrome, Angelman syndrome, Chudley Lowry syndrome, Cornelia de Lange syndrome, Laron syndrome, Kleeftstra syndrome/9q34.3, Camera-Marugo-Cohen syndrome, Clark and Baraitser XLMR syndrome, DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, 22q11.2 deletion syndrome, rapid onset obesity with hypothalamic
15 dysfunction (ROHHAD), rapid onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and neural crest tumor (ROHHAD NET), Shashi XLMR syndrome, mental retardation, epileptic seizures, hypogonadism and -genitalism, microcephaly, obesity (MEHMO) syndrome, mandibular prognathism with eye and skin anomalies (MOMES) syndrome, and MOMO syndrome.
20 Additional diseases, disorders, or conditions that may be treated by administration of an MC4R agonist, e.g., an MC4R agonist described herein, include those summarized in Kaur et al (2017) Obesity Reviews 18:603-634.

Outcomes

25 In embodiments, methods described herein result in one or more outcomes, including a reduction of weight (e.g., body weight), a reduction in hunger level, no detectable decrease in energy expenditure (e.g., resting energy expenditure), an increase in energy expenditure (e.g., resting energy expenditure), a reduction in daily/weekly/monthly food intake, a reduction in waist circumference, no detectable
30 increase in blood pressure, or a reduction in blood pressure in a subject, e.g., relative to a control.

In embodiments, the control is the measurement of the parameter in the subject prior to administration of (treatment with) a MC4R agonist. In embodiments, the control is a predetermined value, e.g., the value of the parameter in an average obese human population, e.g., of like age and gender as the subject; or the value of the parameter measured in the
5 subject at a previous time point (e.g., at a previous visit, e.g., to a physician, medical facility or laboratory).

In embodiments, the outcome (e.g., the reduction, increase, no detectable decrease, or no detectable increase in a given parameter) is measured in the subject 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment with a MC4R agonist. In other embodiments, the outcome (e.g., the reduction, increase, no detectable decrease, or no detectable increase in a given parameter) is measured in the subject over a period of time (e.g., over a period of 1-2 weeks, 2-4 weeks, 4-6 weeks, 6-8 weeks, 8-12 weeks, or 12-16 weeks) during a course of treatment.

In embodiments, methods described herein result in a reduction of weight (e.g., body weight) in the subject compared to a control (e.g., weight of the subject before treatment or a predetermined value, e.g., average weight of an obese human population of like age and gender as the subject not subjected to therapeutic intervention, or the weight of the subject at a previous measurement, e.g., at a previous visit). In embodiments, the reduction is about 1 kg to 3 kg after 1 week of treatment, about 1 kg to 6 kg after 2 weeks of treatment, about 2 kg to 12 kg after 4 weeks of treatment, about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment. In embodiments, the reduction is at a rate of loss of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment, or 16-32 weeks of treatment, or longer.

25 Measurement of weight, e.g., body weight, can be performed using standard methods in the art.

In embodiments, the reduction in weight is characterized by a percentage change in the subject's weight, e.g., body weight, compared to a control (e.g., the percentage change in weight, e.g., body weight, of the subject before treatment or a predetermined value, e.g., the
30 percentage change from the average weight of an obese human population of like age and

gender as the subject not subjected to therapeutic intervention, or the percentage change from the weight of the subject at a previous measurement, e.g., at a previous visit).

A subject may experience a reduction in weight upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience a reduction in weight of greater than 1% upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12.5%, 15%, 17.5%, 20%, 22.5%, 25%, 30%, 35%, 40%, or more relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 2% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 3% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 4% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 6% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 7% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 8% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight

of greater than 9% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 10% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 12.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 15% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 17.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 20% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 22.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 25% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 30% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 35% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of greater than 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in weight greater than 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in weight between about 1% to about 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 35% , 1% to about 30%, 1% to about 25%, 1% to about 22.5%, 1% to about 20%, 1% to about 17.5%, 1% to about 15%, 1% to about 12.5%, 1% to about 10%, 1% to about 9%, 1% to about 8%, 1% to about 7%, 1% to about 6%, 1% to about 5%, 1% to about 4%, 1% to about 3%, or between 1% to about 2% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 35% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 30% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 25% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 22.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 20% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 17.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 15% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight

of between about 1% to about 12.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 10% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 9% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 8% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 7% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 6% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 4% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 3% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 1% to about 2% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in weight of between about 5% to about 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 35%, 5% to

about 30%, 5% to about 25%, 5% to about 22.5%, 5% to about 20%, 5% to about 17.5%, 5% to about 15%, 5% to about 12.5%, 5% to about 10%, 5% to about 9%, 5% to about 8%, 5% to about 7% or between about 5% to about 6% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 35% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 30% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 25% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 22.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 20% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 17.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 15% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 12.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 10% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g.,

SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 9% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 8% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 7% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of between about 5% to about 6% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in BMI between about 10% to about 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 35%, 10% to about 30%, 10% to about 25%, 10% to about 22.5%, 10% to about 20%, 10% to about 17.5%, 10% to about 15%, or between about 10% to about 12.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 35% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 30% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 25% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 22.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about

10% to about 20% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 17.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 15% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 10% to about 12.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in weight between about 20% to 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 20% to about 35%, 20% to about 30%, 20% to 25%, or between about 20% to about 22.5% relative to the weight of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to 35% relative to the weight of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to 30% relative to the weight of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to 25% relative to the weight of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to 22.5% relative to the weight of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in weight between about 20% to 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 20% to about 39%, 20% to about 38%, 20%

to about 37%, 20% to about 36%, 20% about 35%, 20% to about 34%, 20% to about 33%,
20% to about 32%, 20% to about 31%, 20% about 30%, 20% to 29%, 20% to about 28%,
20% to about 27%, 20% to about 26%, 20% to about 25%, 20% to about 24%, 20% to about
23%, 20% to about 22%, or between about 20% to about 21% relative to the weight of the
5 subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein,
e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight
between about 20% to about 39% relative to the weight of the control prior to administration
of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an
embodiment, the subject experiences a reduction in weight between about 20% to about 38%
10 relative to the weight of the control prior to administration of the MC4R agonist (e.g., an
MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject
experiences a reduction in weight between about 20% to about 37% relative to the weight of
the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described
herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in
15 weight between about 20% to about 36% relative to the weight of the control prior to
administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID
NO: 140). In an embodiment, the subject experiences a reduction in weight between about
20% to about 35% relative to the weight of the control prior to administration of the MC4R
agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment,
20 the subject experiences a reduction in weight between about 20% to about 34% relative to the
weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist
described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a
reduction in weight between about 20% to about 33% relative to the weight of the control
prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g.,
25 SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between
about 20% to about 32% relative to the weight of the control prior to administration of the
MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an
embodiment, the subject experiences a reduction in weight between about 20% to about 31%
relative to the weight of the control prior to administration of the MC4R agonist (e.g., an
30 MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject
experiences a reduction in weight between about 20% to about 30% relative to the weight of

the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 29% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 28% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 27% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 26% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 25% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 24% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 23% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 22% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 20% to about 21% relative to the weight of the control prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in weight between about 30% to about 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 35% relative to the

weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in weight between about 30% to about 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 39%, 30% to about 38%, 30% to about 37%, 30% to about 36%, 30% to about 35%, 30% to about 34%, 30% to about 33%, 30% to about 32% or between about 30% to about 31% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 39% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 38% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 37% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 36% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 35% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 34% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 33% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight between about 30% to about 32% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences

a reduction in weight between about 30% to about 31% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an agonist described herein, e.g., SEQ ID NO: 140).

5 In an embodiment, the subject experiences a reduction in weight of less than 40% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 35 %, 30%, 25%, 22.5%, 20%, 17.5%, 15%, 12.5%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 35% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 30% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 25% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 22.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 20% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 17.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 15% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 12.5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 10% relative to the weight of the subject prior to administration of the MC4R

agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 9% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 8% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 7% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 6% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 5% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 4% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 3% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 2% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in weight of less than 1% relative to the weight of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In embodiments, methods described herein result in a reduction in body mass index (BMI), measured in kg/m^2 , in the subject compared to a control (e.g., BMI of the subject before treatment or a predetermined value, e.g., average BMI of an obese human population of like age and gender as the subject not subjected to therapeutic intervention, or the BMI of the subject at a previous measurement, e.g., at a previous visit.)

A subject may experience a reduction in BMI upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the

subject may experience a reduction of BMI greater 1% upon administration of the MC4R agonist(e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140), relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 1.5%, 2%, 2.5%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12.5%, 15%, 17.5%, 20% or more, relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 2% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 5% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 7.5% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 10% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 15% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 18% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 19% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of greater than 20% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in BMI between about 1% to about 20% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 1% to about

19%, 1% to about 18%, 1% to about 17%, 1% to about 16%, 1% to about 15%, about 1% to about 12.5%, about 1% to about 10%, about 1% to about 7.5%, about 1% to about 5% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 1% to about 15% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 1% to about 10% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in BMI between about 5% to about 20% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 5% to about 19%, 5% to about 18%, 5% to about 17%, 5% to about 16%, 5% to about 15%, about 5% to about 12.5%, about 5% to about 10%, about 5% to about 7.5% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 5% to about 15% relative to the BMI of the subject prior to administration of the MC4R agonist. In an embodiment, the subject experiences a reduction in BMI between about 5% to about 10% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in BMI between about 10% to about 20% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 10% to about 19%, 10% to about 18%, 10% to about 17%, 10% to about 16%, 10% to about 14%, 10% to about 13%, 10% to about 12%, or 10% to 11% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 10% to about 19% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject

experiences a reduction in BMI between about 10% to about 18% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 10% to about 17% relative to the BMI of the

5 subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 10% to about 16% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI

10 between about 10% to about 15% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 10% to about 14% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI

15 between about 10% to about 13% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI between about 10% to about 12% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI

20 between about 10% to about 11% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

25 A subject may experience a reduction in BMI upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience a reduction of BMI of less than 20% upon administration of the MC4R agonist relative to the BMI of the subject prior to administration of the MC4R agonist. In an embodiment, the subject experiences a

30 reduction in BMI of less than 17.5%, 15%, 12.5%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2.5%, 2%, 1.5% or less, relative to the BMI of the subject prior administration of

the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 17.5% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a

5 reduction in BMI of less than 15% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 12.5% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a

10 reduction in BMI of less than 10% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 9% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in

15 BMI of less than 8% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 7% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less

20 than 6% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 5% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 4%

25 relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 3% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI of less than 2% relative to the BMI

30 of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in

BMI of less than 1% relative to the BMI of the subject prior to administration of the MC4R agonist (e.g., a MC4R agonist described herein, e.g., SEQ ID NO: 140).

In embodiments, methods described herein result in a reduction of BMI Z-Score in the subject compared to the BMI Z-Score of a control (e.g., the BMI Z-Score of the subject before treatment or a predetermined value, e.g., average BMI Z-Score of an obese human population of like age and/or gender as the subject not subjected to therapeutic intervention, or the BMI Z-Score of the subject at a previous measurement, e.g., a previous measurement), wherein the Z-Score is computed from the standard deviation from a reference population of similar age and gender (e.g., the Z-Score of a reference population with a mean BMI of 25 and a standard deviation of 1.5).

A subject may experience a reduction in BMI Z-Score upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience a reduction in BMI Z-Score of 0.1 upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140), relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist. In an embodiment, the subject experiences a reduction of BMI Z-Score of greater than 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.25, 2.5, 2.75, 3, or more, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist. In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.2, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.3, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.4, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.5, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In

an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.6, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.7, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.8, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 0.9, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.1, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.2, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.3, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.4, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.5, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.6, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.7, relative to the BMI Z-Score of the subject prior to administration of the MC4R

agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.8, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an

5 embodiment, the subject experiences a reduction in BMI Z-Score greater than 1.9, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 2, relative to the BMI Z-Score of the subject prior to administration of the MC4R

10 agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 2.25, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 2.5,

15 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score greater than 2.75, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140). In an

20 embodiment, the subject experiences a reduction in BMI Z-Score greater than 3, relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described here, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 3 relative to the BMI Z-Score of the subject prior to

25 administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 2.75, 0.1 to about 2.5, 0.1 to about 2.25, 0.1 to about 2, 0.1 to about 1.9, 0.1 to about 1.8, 0.1 to about 1.7, 0.1 to about 1.6, 0.1 to about 1.5, 0.1 to about 1.4, 0.1 to about 1.3, 0.1 to about 1.2, 0.1 to about 1.1, 0.1 to

30 about 1, 0.1 to about 0.9, 0.1 to about 0.8, 0.1 to about 0.7, 0.1 to about 0.6, 0.1 to about 0.5, 0.1 to about 0.4, 0.1 to about 0.3, or between 0.1 to about 0.2 relative the

BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 2.75 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 2.5 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 2.25 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 2 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.9 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.8 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.7 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.6 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.5 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.4 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about

1.3 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.2 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1.1 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 1 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.9 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.8 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.7 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.6 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.5 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.4 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.3 relative to the BMI Z-Score of the subject prior to administration of the

MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 0.1 to about 0.2 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

- 5 In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to 3 relative the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of between about 1 to about 2.75, 1 to about 2.5, 1 to about 2.25, 1 to about 2, 1 to about 1.9, 1 to about 1.8, 1 to about 1.7, 1 to about 1.6, 10 1.5, 1 to about 1.4, 1 to about 1.3, 1 to about 1.2, or between 1 to about 1.1 relative to the BMI Z-Score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 2.75 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, 15 e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 2.5 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 2.25 relative to the BMI Z-Score of the subject prior to administration of the 20 MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 2 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.9 relative to the BMI Z- 25 Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.8 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z- 30 Score between about 1 to about 1.7 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID

- NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.6 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.5 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.4 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.3 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.2 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 1 to about 1.1 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).
- 20 In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 3 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.75, 2 to about 2.5, or between about 2 to about 2.25 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.75 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.5 relative to the BMI Z-Score of the subject prior to administration of the

MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.25 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

5 In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 3 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.9, 2 to about 2.8, 2 to about 2.7, 2 to about 2.6, 2 to about 2.5, 2 to about 2.4, 2 to about 2.3, 2 to about 2.2
10 or between 2 to about 2.1 relative the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.9 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the
15 subject experiences a reduction in BMI Z-Score between about 2 to about 2.8 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.7 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein,
20 e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.6 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.5 relative to the BMI Z-Score of the subject prior to administration of the
25 MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.4 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.3 relative to the
30 BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences

a reduction in BMI Z-Score between about 2 to about 2.2 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score between about 2 to about 2.1 relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

A subject may experience a reduction in BMI Z-Score upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience a reduction in BMI Z-Score of less than 3 upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 2.9, 2.75, 2.5, 2.25, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2 or less relative to the BMI Z-Score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 2.9 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 2.75 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 2.25 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 2 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.9 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.8 relative to the BMI Z-Score of the of the subject prior to

administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.7 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.6 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.5 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.4 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.3 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.2 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1.1 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 1 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.9 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.8 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.7 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described

herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.6 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.5 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.4 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.3 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in BMI Z-Score of less than 0.2 relative to the BMI Z-Score of the of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In embodiments, the hunger level is characterized by a weekly average of the daily most hunger score, wherein the weekly average of the daily most hunger score in a subject is compared to a control (e.g., the weekly average of the daily most hunger score in a subject before treatment or a predetermined value, e.g., the mean of the weekly average of the daily most hunger score of an obese human population of like age and gender as the subject not subjected to therapeutic intervention, or the weekly average of the daily most hunger score of the subject at a previous measurement, e.g., a previous visit).

A subject may experience a reduction in the weekly average of the daily most hunger score upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience a reduction in the weekly average of the daily most hunger score greater than 0.1 upon administration of the MC4R agonist relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, a subject

experiences a reduction in the weekly average of the daily most hunger score greater than 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.2, 1.4, 1.6, 1.8, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 or greater relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.3 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.7 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.8 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 0.9 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described

herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 1 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 1.2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 1.4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 1.6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 1.8 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 2.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 3 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of

the daily most hunger score greater than 3.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 4.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 5.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 6.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 7 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score greater than 7 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 7 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 6.5, 0.1 to about 6, 0.1 to about 6, 0.1 to about 5.5, 0.1 to about 5, 0.1 to about 4.5, 0.1 to about 4, 0.1 to about 3.5, 0.1 to about 3, 0.1 to about 2.5, 0.1 to about 2, 0.1 to about 1.8, 0.1 to about 1.6, 0.1 to about 1.4, 0.1 to about 1.2, 0.1 to about 1, 0.1 to about 0.9, 0.1 to about 0.8, 0.1 to about 0.7, 0.1 to about 0.6, 0.1 to about 0.5, 0.1 to about 0.4, 0.1 to about 0.3, or 0.1 to about 0.2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 6.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 5.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 4.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 4 relative to the weekly

average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 3.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 3 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 2.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 1.8 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 1.6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 1.4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 1.2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the

weekly average of the daily most hunger score between about 0.1 to about 1 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most

5 hunger score between about 0.1 to about 0.9 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about

10 0.8 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 0.7 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject

15 experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 0.6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 0.5 relative to the weekly

20 average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 0.4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described

25 herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 0.1 to about 0.3 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most

30 hunger score between about 0.1 to about 0.2 relative to the weekly average of the daily most

hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

5 In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 7 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 6.5, 1 to about 6, 1 to about 5.5, 1 to about 5, 1 to about 4.5, 1 to about 4, 1 to about 3.5, 1 to about 3, 1 to about 2.5, 1 to about 2, 1 to about 1.8, 1 to about 1.6, 1 to about 1.4 or 1 to about 1.2 relative to the
10 weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 6.5 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g.,
15 SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 6 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 5.5
20 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 5 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO:
25 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 4.5 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 4 relative to the daily most
30 hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a

reduction in the weekly average of the daily most hunger score between about 1 to about 3.5 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between

5 about 1 to about 3 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 2.5 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein,

10 e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 2 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 1.8

15 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 1.6 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO:

20 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 1.4 relative to the daily most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 1 to about 1.2 relative to the daily

25 most hunger score of the subject prior to administration of the agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 7 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described

30 herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 6.5, 2 to about 6, 2

to about 5.5, 2 to about 5, 2 to about 4.5, 2 to about 4, 2 to about 3.5, 2 to about 3, or 2 to about 2.5. In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 6.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g.,
5 an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of
10 the daily most hunger score between about 2 to about 5.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 5 relative to the weekly average of the daily most hunger score of the subject prior
15 to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 4.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject
20 experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 3.5 relative to the weekly average of
25 the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 3 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ
30 ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 2 to about 2.5 relative to the weekly average of

the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 7 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 6.5, 3 to about 6, 3 to about 5.5, 3 to about 5, 3 to about 4.5, 3 to about 4, or 3 to about 3.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 6.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 6 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 5.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 4.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 3 to about 4 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score

between about 3 to about 3.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

5 In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 4 to about 7 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 4 to about 6.5, 4 to about 6, 4 to about 5.5, 4 to about 5, or 4 to about 4.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 4 to about 6.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 4 to about 6 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 4 to about 5.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 4 to about 5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 4 to about 4.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

20 In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 5 to about 7 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the

weekly average of the daily most hunger score between about 5 to about 6.5, 5 to about 6, or 5 to about 5.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 5 to about 6.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 5 to about 6 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 5 to about 5.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 6 to about 7 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score between about 6 to about 6.5 relative to the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 7 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In embodiments, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 6.5, 6, 5.5, 5, 4.5, 4, 3.5, 3., 2.5, 2., 1.8, 1.6, 1.4, 1.2, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1 or less relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 6.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described

herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 5.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 4.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 3.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 3 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 2.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an

embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 1.8 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 1.6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 1.4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 1.2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 1 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.9 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.8 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.7 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.6 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences

a reduction in the weekly average of the daily most hunger score of less than 0.5 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.4 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.3 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.2 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in the weekly average of the daily most hunger score of less than 0.1 relative to the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In embodiments, methods described herein result in an improvement in the IWQOL or IWQOL-Lite Quality of life score of the subject compared to a control (e.g., IWQOL or IWQOL-Lite score of the subject prior to treatment or a predetermined value, e.g., average IWQOL or IWQOL-Lite score of an obese human population of similar age and gender as the subject not subjected to therapeutic intervention, or the IWQOL or IWQOL-Lite score of the subject at a previous measurement, e.g., at a previous visit).

A subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 5 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40 points or

more relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 6 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 7 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 8 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 9 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 10 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 12 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 14 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 16 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the

IWQOL or IWQOL-Lite Quality of Life score greater than 18 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score

5 greater than 20 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 25 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R

10 agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 30 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the

15 IWQOL or IWQOL-Lite Quality of Life score greater than 35 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). For example, the subject may experience an improvement in the IWQOL or IWQOL-Lite Quality of Life score greater than 40 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the

20 subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140).

In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 40 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R

25 agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 35 points, 5 to about 30 points, 5 to about 25 points, 5 to about 20 points, 5 to about 18 points, 5 to about 16 points, 5 to about 14 points, 5 to about 12 points, 5 to about 10 points, 5 to about 9 points, 5 to about 8 points, 5 to

30 about 7 points, 5 to about 6 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist

described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 35 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 30 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 25 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 20 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 18 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 16 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 14 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 12 points relative to the IWQOL or IWQOL-Lite Quality of Life

score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 10 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 9 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 8 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 7 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 5 to about 6 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 40 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 35 points, 10 to about 30 points, 10 to about 25 points, 10 to about 20 points, 10 to about 18 points, 10 to about 16 points, 10 to about 14 points, or 10 to about 12 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 35 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

5 MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 30 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

10 MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 25 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

15 MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 20 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

20 MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 18 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

25 MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 16 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

30 MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 14 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an

MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 10 to about 12 points relative to the IWQOL or IWQOL-Lite

Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140).

5 In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 20 to about 40 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 20 to about 35 points, 20 to about 30 points, or 20 to about 25 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 20 to about 35 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 20 to about 30 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 20 to about 25 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140).

25 In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 30 to about 40 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score between about 30 to about 35 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140).

MC4R agonist (e.g., an MC4R agonist described herein, e.g., an MC4R agonist, e.g., SEQ ID NO: 140).

- In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 40 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 35 points, 30 points, 25 points, 20 points, 18 points, 16 points, 14 points, 12 points, 10 points, 9 points, 8 points, 7 points, 6 points or less relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 35 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 30 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 25 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 20 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 18 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 16 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an

MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 14 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 12 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 10 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 9 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 8 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 7 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences an improvement in the IWQOL or IWQOL-Lite Quality of Life score less than 6 points relative to the IWQOL or IWQOL-Lite Quality of Life score of the subject prior to the administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140).

In embodiments, methods described herein result in a reduction in hunger level in the subject compared to a control (e.g., hunger level of the subject before treatment or a predetermined hunger level, e.g., average hunger level of an obese human population of like age and gender as the subject or the hunger level of the subject at a previous measurement, e.g., at a previous visit). In embodiments, the methods described herein result in abolishment of hunger in the subject.

In embodiments, hunger is measured by a scale, such as a Likert hunger scale, which ranges from 0 to 10 and is described herein. In embodiments, methods described herein result in a reduction in hunger score in the subject compared to a control (e.g., hunger level of the subject before treatment or a predetermined hunger level, e.g., average hunger level of an obese human population of like age and gender as the subject or the hunger level of the subject at a previous measurement, e.g., at a previous visit). In embodiments, methods described herein result in a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points, compared to the control (e.g., hunger level of the subject before treatment or a predetermined hunger level, e.g., average hunger level of an obese human population of like age and gender as the subject or the hunger level of the subject at a previous measurement, e.g., at a previous visit). In embodiments, methods described herein result in a score of 0 on the Likert hunger scale after treatment.

In embodiments, the reduction in hunger level is measured/observed after 1 to 2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer.

REE is a measure of the basal metabolic rate of the subject and can be determined using methods such as those described in Chen et al. *J. Clin. Endocrinol. Metab.* 100.4(2015):1639-45. In embodiments, the REE can be determined by placing the subject in a whole-room indirect calorimeter (also called a metabolic chamber) at a certain time after treatment (e.g., after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks). In embodiments, the REE is measured in 30-minute measurements periods, and in some cases, REE values from several 30-minute periods are averaged to generate an average REE. In embodiments, the REE can be determined after a 10-12 hour fasting period, at thermoneutrality (e.g., around 25 deg C), where the subject is awake without psychological or physical stress. In embodiments, REE is measured in units of energy per unit time (e.g., kcal/h or kcal/day). In embodiments, the REE is measured relative to kg lean body mass in a subject (e.g., REE/kg lean mass), e.g., as described in the Examples.

In embodiments, methods described herein result in no change or no decrease in energy expenditure, e.g., resting energy expenditure (REE), in the subject over an

hourly, daily (e.g., in 24 hours), weekly (e.g., in 7 days), or monthly (e.g., in 30 days) period compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., average REE of an obese human population of like age and gender and normalized for weight as the subject or the REE of the subject at a previous measurement, e.g., previous visit), e.g., as measured after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks of treatment.

5 In embodiments, methods described herein result in no detectable change or no detectable decrease in energy expenditure, e.g., resting energy expenditure (REE) per kg lean body mass, in the subject over an hourly, daily (e.g., in 24 hours), weekly (e.g., in 7 days), or monthly (e.g., in 30 days) period compared to the control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., average REE of an obese human population of like age and gender as the subject or the REE of the subject at a previous measurement, e.g., previous visit), e.g., as measured after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks of treatment.

15 In embodiments, methods described herein result in an increase in energy expenditure, e.g., resting energy expenditure (REE), in the subject over a hourly, daily (e.g., in 24 hours), weekly (e.g., in 7 days), or monthly (e.g., in 30 days) period compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., average REE of an obese human population of like age and gender and normalized for weight as the subject or the REE of the subject at a previous measurement, e.g., previous visit), e.g., as measured after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks of treatment.

In embodiments, the increase in REE in the subject is at least 20 kcal/day (e.g., at least 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 kcal/day or more), e.g., as measured after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks of treatment.

25 In embodiments, the increase in REE in the subject is at least 2% (e.g., at least 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or more), e.g., as measured after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks of treatment, compared to the REE in the subject prior to treatment.

30 In embodiments, the REE in the subject (e.g., adult subject) after treatment with a MC4R agonist (e.g., after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks of treatment) is at least 1800 kcal/day (e.g., at least 1800, 1825, 1850, 1875, 1900, 1925, 1950, 1975, 2000, 2025, 2050, 2100, 2150, 2200, 2250, 2300, 2400 kcal/day, or more), e.g., for an adult subject.

In embodiments, the REE in the subject (e.g., pediatric subject) after treatment with a MC4R agonist (e.g., after 3, 4, 5, 6, 7 days, or 1, 2, 3, 4, or more weeks of treatment) is at least 200 kcal/day (e.g., at least 200, 225, 250, 275, 300, 325, 350, 375, 400, 450, 500 kcal/day or more), e.g., for pediatric patients.

- 5 In embodiments, methods described herein result in a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level, e.g., the food intake of an average human obese population or the food intake of the subject at a previous measurement, e.g., at a previous visit), e.g., where the food intake is measured as daily food intake
- 10 or food intake over a period of 24 hours, or one week,. In embodiments, the reduction is at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, e.g., for daily food intake or food intake over a period of 24 hours, or one week, or 30 days or for longer time periods, e.g., for an adult subject.
- 15 In embodiments, mean food intake can decrease from a baseline at or above about 100 kcal/kg/day to about 90, 80, 70, 60, 50, 40, 30, 20 or 10 kcal/kg/day or lower after treatment with a MC4R agonist, e.g., setmelanotide, e.g., in a pediatric subject at about 1 year of age. In embodiments, mean food intake can decrease from a baseline at or above about 40 kcal/kg/day to about 35, 30, 20 or 10 kcal/kg/day or lower after
- 20 treatment with a MC4R agonist, e.g., setmelanotide, e.g., in a pediatric subject in late adolescence.

Food intake can be determined by standard methods, e.g., as described in Rutishauser. Pub. Health Nutr. 8.7A(2005):1100-07.

- 25 In embodiments, methods described herein result in a reduction in waist circumference of the subject compared to a control (e.g., the waist circumference of the subject prior to treatment or the waist circumference of the subject at a previous measurement, e.g., previous visit), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

- 30 In embodiments, the reduction in waist circumference is at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject (e.g., adult subject) compared to a control (e.g., the waist circumference of the subject prior to treatment or a

predetermined waist circumference, e.g., the waist circumference of an average obese human population of like age and gender or the waist circumference of the subject at a previous measurement, e.g., previous visit), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

- 5 In embodiments, the waist circumference is measured using standard methods. In embodiments, the waist circumference is the largest circumference around a subject's mid-section, e.g., around a subject's abdomen. In other embodiments, the waist circumference is measured around the natural waist (e.g., in between the lowest rib and the top of the hip bone), the umbilicus, or at the narrowest point of the midsection.
- 10 A subject may experience a reduction in waist circumference upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). For example, the subject may experience a reduction in waist circumference of greater than 1 cm upon administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140) relative to the waist circumference of the subject prior to administration of the
- 15 agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10 cm or more relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 1.5
- 20 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 2 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject
- 25 experiences a reduction in waist circumference of greater than 2.5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 3 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described
- 30 herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 4 cm relative to the waist circumference of the subject

prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 6 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of greater than 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference of greater than 10" relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 9 cm, 1 to about 8 cm, 1 to about 7 cm, 1 to about 6 cm, 1 to about 5 cm, 1 to about 4 cm, 1 to about 3 cm, or 1 to about 2 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in

- waist circumference between about 1 to about 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 8 cm relative to the waist circumference of the
- 5 subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist
- 10 circumference between about 1 to about 6 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein,
- 15 e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 4 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 3 cm relative to the waist circumference of the
- 20 subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 1 to about 2 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).
- 25 In an embodiment, the subject experiences a reduction in waist circumference between about 2 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 2 to about 9 cm, 2 to about 8 cm, 2 to about 7 cm, 2 to about 6 cm, 2 to about
- 30 5 cm, 2 to about 4 cm, or 2 to about 3 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g.,

SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 2 to about 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist
5 circumference between about 2 to about 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 2 to about 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein,
10 e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 2 to about 6 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 2 to about 5 cm relative to the waist circumference of the
15 subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 2 to about 4 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist
20 circumference between about 2 to about 3 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 10 cm relative to the waist circumference of the subject prior to
25 administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 9 cm, 3 to about 8 cm, 3 to about 7 cm, 3 to about 6 cm, 3 to about 5 cm, or 3 to about 4 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID
30 NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 9 cm relative to the waist circumference of the subject prior to

administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 6 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 3 to about 4 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 4 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 4 to about 9 cm, 4 to about 8 cm, 4 to about 7 cm, 4 to about 6 cm, or 4 to about 5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 4 to about 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 4 to about 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 4 to

about 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 4 to about 6 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 4 to about 5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 5 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 5 to about 9 cm, 5 to about 8 cm, 5 to about 7 cm, or 5 to about 6 cm, relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 5 to about 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 5 to about 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 5 to about 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 5 to about 6 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 6 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference

between about 6 to about 9 cm, 6 to about 8 cm, or 6 to about 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 6 to about 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 6 to about 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 6 to about 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 7 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 7 to about 9 cm or about 7 to about 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 7 to about 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 7 to about 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 8 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference between about 8 to about 9 cm relative to the waist circumference of the subject prior to

administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference between about 9 to about 10 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In an embodiment, the subject experiences a reduction in waist circumference of less than 10" relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of less than 9, 8, 7, 6, 5, 4, 3, 2.5, 2, 1.5, 1 cm or less relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). In an embodiment, the subject experiences a reduction in waist circumference of less than 9 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 8 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 7 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 6 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 4 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 3 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist

circumference of less than 2.5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 2 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 1.5 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140). the subject experiences a reduction in waist circumference of less than 1 cm relative to the waist circumference of the subject prior to administration of the MC4R agonist (e.g., an MC4R agonist described herein, e.g., SEQ ID NO: 140).

In embodiments, methods described herein result in no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to a control blood pressure (e.g., the blood pressure of the subject prior to treatment or a predetermined blood pressure, e.g., the blood pressure of an average obese human population of like age and gender or the blood pressure of the subject at a previous measurement, e.g., previous visit), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In embodiments, methods described herein result in a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject a control blood pressure (e.g., the blood pressure of the subject prior to treatment or a predetermined blood pressure, e.g., the blood pressure of an average obese human population of like age and gender or the blood pressure of the subject at a previous measurement, e.g., previous visit), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In embodiments, the reduction in blood pressure, e.g., systolic blood pressure, is at least 3 mmHg (e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In embodiments, the reduction in blood pressure, e.g., diastolic blood pressure, is at least 4 mmHg (e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In embodiments, the methods described herein do not result in an adverse effect on heart rate or blood pressure.

- In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises
- 5 administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences one or more of:
- (i) a BMI reduction $\geq 5\%$ after 16 weeks from baseline for all subjects
 - 10 (ii) A mean reduction in BMI $\geq 10\%$ after 16 weeks from baseline for a subject completing the course of therapy
 - (iii) a mean reduction in BMI of about 6.36 after 16 weeks from baseline
 - (iv) a mean reduction in BMI of about 7.16 after 16 weeks from baseline, wherein the subject is a pediatric patient from 6 to less than 18 years of age
 - 15 (v) a mean reduction in BMI of about 2.75 after 16 weeks from baseline, wherein the subject is an adult subject
 - (vi) a mean percentage reduction in BMI of about 17.18% after 16 weeks from baseline
 - (vii) A mean reduction in BMI Z-Score of about 1.08 after 16 weeks from baseline
 - (viii) A mean reduction in weight of about 15.87 kg after 16 weeks from baseline
 - 20 (ix) A mean reduction in weight of about 17.83 kg after 16 weeks from baseline, wherein the subject is a pediatric patient from 6 to less than 18 years of age
 - (x) A mean reduction in weight of 7.02 kg after 16 weeks from baseline, wherein the subject is an adult patient
 - (xi) A mean percentage reduction in weight of 15.79% after 16 weeks from baseline
 - 25 (xii) A mean percentage reduction in weight of 17.80% after 16 weeks from baseline, wherein the subject is a pediatric patient from 6 to less than 18 years of age
 - (xiii) A mean percentage reduction in weight of 6.76% after 16 weeks from baseline, wherein the subject is an adult subject
 - (xiv) A mean reduction in the weekly average of the daily most hunger score of 2.66 after 16
 - 30 weeks from baseline

- In yet another embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-e)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences one or more of:
- (xvi) a BMI reduction $\geq 5\%$ after 16 weeks from baseline for all subjects
 - (xvii) A mean reduction in BMI $\geq 10\%$ after 16 weeks from baseline for a subject completing the course of therapy
 - 10 (xviii) a mean reduction in BMI of about 5.32 after 16 weeks from baseline
 - (xxi) a mean percentage reduction in BMI of about 14.46% after 16 weeks from baseline
 - (xxii) A mean reduction in the weekly average of the daily most hunger score of 2.77 after 16 weeks from baseline

- In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences all of (i) –(xiv).

- In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences all of (xvi) –(xii).

- In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences all of (i) –(xxii).

- In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula

XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences one or more of (iv), (vii), (ix), (xii).

5 In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences all of (iv), (vii), (ix), (xii).

10 In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences one or more of (v), (x) and (xiii).

15 In an embodiment, the present disclosure provides a method for treating obesity, e.g., hypothalamic obesity, in a subject, wherein the method comprises administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-e)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and (XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences all of (v), (x) and (xiii).

Patient Selection

In accordance with any method described herein, in certain embodiments, the subject is obese, e.g., prior to administration of an MC4R agonist described herein, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration of the MC4R agonist. In embodiments, the subject is a severely obese, pediatric or adult patient e.g., prior to administration of an MC4R agonist described herein, e.g., at the time the MC4R agonist is prescribed or at the time of the first administration of the MC4R agonist. In embodiments, the subject is hyperphagic, e.g., prior to administration of an MC4R agonist described herein, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration of the MC4R agonist.

In embodiments, the subject (e.g., adult subject) has a body mass index (BMI) greater than 25 kg/m^2 or 30 kg/m^2 (e.g., $\geq 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 \text{ kg/m}^2$ or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

In embodiments, the subject (e.g., pediatric subject) has a body mass index (BMI) higher than 85-95 percentile prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

In embodiments, the subject has a body weight of at least about 5 kg, e.g., at least about 5 kg, 10 kg, 20kg, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 200, 205, 210, 215, 220 kg or greater, e.g., prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In embodiments, the subject has a body weight of a least 20 kg, at least 60 kg, or at least 100 kg, e.g., prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

In embodiments, the subject has received intervention in the gastrointestinal system. For example, the subject may have received a gallbladder surgery, an intestinal surgery, a gastric surgery (e.g., a bariatric surgery), or other survival procedure. In an embodiment, the subject has received a gastric bypass surgery. In an embodiment, the subject has received a surgery resulting in a restriction of the total amount of food capable of being held or processed at one time, e.g., the stomach, small intestine, large intestine, or colon.

In an embodiment, the subject has undergone a surgery, e.g., a tumor resection surgery.

In an embodiment, the subject has a proliferative brain disease. The proliferative brain disease may include a benign tumor, benign lesion, or a malignant tumor, e.g., cancer. In an embodiment, the proliferative brain disease is present in the hypothalamus. In an embodiment, the proliferative brain disease is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or arcuate hypothalamic nucleus.

In an embodiment, the proliferative brain disease is a benign brain tumor or benign brain lesion. Exemplary types of benign tumors or brain lesions include a meningioma, pituitary adenoma, craniopharyngioma, Schwannoma, nasopharyngeal angiofibroma, choroid

plexus tumor, dysembryoplastic neuroepithelial tumor, neurofibroma, hemangioblastoma, chondroma, giant cell tumor, osteoma, arachnoid cyst, colloid cyst, dermoid cyst, epidermoid cyst, fibrous dysplasia, Rathke's cleft cyst, and petrous apex lesion. In an embodiment, the proliferative brain disease is a
 5 craniopharyngioma.

In an embodiment, the subject has a malignant tumor or a cancer, e.g., a cancer of the central nervous system or peripheral nervous system. In an embodiment, the cancer is present in the hypothalamus. In an embodiment, the cancer is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or
 10 arcuate hypothalamic nucleus. In an embodiment, the subject has a brain cancer. Exemplary brain cancers include glioblastoma, oligodendroglioma, and astrocytoma. In an embodiment, the cancer comprises astrocytoma. In embodiments, the subject is an adult, e.g., 18 years of age or older, e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51,
 15 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, or older.

In embodiments, the subject is a pediatric subject, e.g., less 18 years of age or younger (e.g., 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 year of age or younger).

In an embodiment, the subject has or is identified as having a metabolic
 20 syndrome. In an embodiment, the subject has or is identified as having diabetes (e.g., Type 2 diabetes).

In embodiments, the subject has or is identified as having a defect, e.g., genetic defect, or a mutation, in an MC4R pathway agonizable gene. In
 25 embodiments, the subject has or is identified as having a mutation a gene selected from the ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBFR, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1,
 30 IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B,

SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, or MeCP2 genes. In embodiments, the subject has a disease or disorder associated with a gene in Table 2. In
 5 embodiments, the subject has or is identified as having a loss of function mutation in one or more genes in Table 2.

In embodiments, the subject does not have or is not identified as having a defect, e.g., genetic defect, or a mutation, in an MC4R pathway agonizable gene. In embodiments, the subject does not have or is not identified as having a mutation a gene selected from the
 10 ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA,
 15 NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, or MeCP2 genes. In embodiments, the subject has a disease or disorder associated with a gene
 20 in Table 2. In embodiments, the subject has or is identified as having a loss of function mutation in one or more genes in Table 2.

In embodiments, methods herein can comprise identifying or selecting a subject having a defect e.g., genetic defect, or a mutation, in one or more genes listed in Table 2. In embodiments, methods herein can comprise acquiring knowledge of the genotype,
 25 predetermined sequence, or mutation. In embodiments, the methods herein can comprise acquiring knowledge of the genotype of, e.g., of a mutation in one or more of ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP,
 30 CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN,

NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, or VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, or MeCP2 genes. In embodiments, the MC4R agonist is administered in response to acquiring knowledge, e.g., detection or identification, of a predetermined sequence, e.g., a mutation, in a gene described herein, one or more of ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, or VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, or MeCP2 genes.

In embodiments, identification or selection of a subject as having a certain genotype or predetermined sequence, e.g., mutation, in a gene, can comprise acquiring knowledge of the certain genotype or predetermined sequence, e.g., mutation. Knowledge of the sort can be acquired in a number of ways, as described in detail in the Definitions section.

In some embodiments, a sequence is acquired, e.g., by obtaining possession of a nucleotide sequence, by “directly acquiring” or “indirectly acquiring” the sequence. “Directly acquiring a sequence” means performing a process (*e.g.*, performing a synthetic or analytical method) to obtain the sequence, such as performing a sequencing method (*e.g.*, a Next Generation Sequencing (NGS) method). “Indirectly acquiring a sequence” refers to receiving information or knowledge of, or receiving, the sequence from another party or source (*e.g.*, a third-party laboratory that directly acquired the sequence). The sequence acquired need not be a full sequence, *e.g.*, sequencing of at least one nucleotide, or obtaining information or knowledge, that

identifies a genotype or predetermined sequence, e.g., mutation, disclosed herein as being present in a subject constitutes acquiring a sequence.

In embodiments, the sequence can be directly acquired. Directly acquiring a sequence includes performing a process that includes a physical change in a physical substance, e.g., a starting material, such as a tissue sample, e.g., a blood sample or tissue biopsy, or analysis of an isolated nucleic acid (e.g., DNA or RNA) sample. Exemplary changes include making a physical entity from two or more starting materials, shearing or fragmenting a substance, such as a genomic DNA fragment; separating or purifying a substance (e.g., isolating a nucleic acid sample from a tissue); combining two or more separate entities into a mixture, performing a chemical reaction that includes breaking or forming a covalent or non-covalent bond. Directly acquiring a value includes performing a process that includes a physical change in a sample or another substance as described above.

In some embodiments, acquiring knowledge of the certain genotype or predetermined sequence, e.g., mutation, can comprise acquiring a sample, e.g., from which the genotype or predetermined sequence, e.g., mutation, is determined. “Acquiring a sample” as the term is used herein, refers to obtaining possession of a sample, e.g., a tissue sample or nucleic acid sample, by “directly acquiring” or “indirectly acquiring” the sample. “Directly acquiring a sample” means performing a process (e.g., performing a physical method such as a surgery or extraction) to obtain the sample. “Indirectly acquiring a sample” refers to receiving the sample from another party or source (e.g., a third-party laboratory that directly acquired the sample). Directly acquiring a sample includes performing a process that includes a physical change in a physical substance, e.g., a starting material, such as a tissue, e.g., a tissue in a human patient or a tissue that has was previously isolated from a patient. Exemplary changes include making a physical entity from a starting material, dissecting or scraping a tissue; separating or purifying a substance (e.g., a sample tissue or a nucleic acid sample); combining two or more separate entities into a mixture; performing a chemical reaction that includes breaking or forming a covalent or non-covalent bond. Directly acquiring a sample includes performing a process that includes a physical change in a sample or another substance, e.g., as described above.

In some aspects, provided herein is also a method of evaluating a subject, e.g., for likely responsiveness to a MC4R agonist, e.g., a MC4R agonist described herein, e.g.,

setmelanotide. In some embodiments, the method comprises acquiring information about the genotype of the subject. In embodiments, the method comprises acquiring information about the presence or absence of a defect, e.g., genetic defect, in one or more genes listed in Table 2 in the subject.

5 In embodiments, the subject can be identified as having a defect, e.g., genetic defect, e.g., mutation, in one or more genes listed in Table 2, using methods described herein.

 In embodiments, the identification of the subject having a defect, e.g., genetic defect, e.g., mutation, indicates that the subject is likely to respond (e.g., with an
10 improvement in one or more symptoms) to a MC4R agonist, e.g., a MC4R agonist described herein, e.g., setmelanotide. In embodiments, an improvement in a symptom can include an outcome described herein. For example, an improvement in a symptom can include a reduction of weight (e.g., body weight), a reduction in hunger level, no detectable decrease in energy expenditure (e.g., resting energy
15 expenditure), an increase in energy expenditure (e.g., resting energy expenditure), a reduction in daily/weekly/monthly food intake, or a reduction in waist circumference, e.g., relative to a control.

 In embodiments, the identification of the subject having the defect, e.g., genetic defect, e.g., mutation, indicates that the subject is more likely to respond to
20 (or is likely to have a greater response to) a MC4R agonist, e.g., a MC4R agonist described herein, e.g., setmelanotide, than a subject (e.g., obese subject, e.g., of like age and/or pre-treatment weight) lacking a genetic defect in one or more genes listed in Table 2, e.g., a wild-type obese subject. In embodiments, a subject that is more likely to respond is more likely to have one or more improved symptoms, such as
25 symptoms described herein, e.g., compared to a control, e.g., a subject (e.g., obese subject, e.g., of like age and/or pre-treatment weight) lacking a genetic defect in one or more genes listed in Table 2, e.g., a wild-type obese subject. In embodiments, a subject that is likely to have a greater response is likely to have a greater
30 improvement in symptoms, e.g., symptoms described herein, e.g., greater weight loss, greater decrease in waist circumference, greater increase in resting energy expenditure, greater decrease in food intake, greater decrease in hunger level, e.g.,

compared to a control, e.g., a subject (e.g., obese subject, e.g., of like age and/or pre-treatment weight) lacking a genetic defect in one or more genes listed in Table 2, e.g., a wild-type obese subject.

In embodiments, methods described herein further comprise providing a report that identifies the presence or absence of the genetic defect and in some cases an identifier for the subject. In embodiments, the report provides a recommendation on potential therapeutic options, likely effectiveness of a therapeutic option, and/or recommendations/instructions for administration of the therapeutic option (e.g., MC4R agonist, e.g., MC4R agonist described herein, e.g., setmelanotide).

MC4R agonists

Described herein are methods for the treating a non-genetic obesity in a subject, comprising administering to a subject a melanocortin 4 receptor (MC4R) agonist. Examples of naturally occurring MC4R agonists include α -MSH, β -MSH, γ -MSH and adenocorticotrophic hormone (ACTH) or a functional fragment thereof. Examples of synthetic MC4R agonists are described in detail below.

In some embodiments, an MC4R agonist can be any known agonist of MC4R. In some example embodiment, the MC4R agonist is not an adrenocorticotrophic hormone (ACTH) or a fragment thereof. Exemplary MC4R agonists include those described in WO2011104378; WO2011104379; WO201060901; WO200887189, WO200887188, WO200887187, WO200887186; US20110065652; WO2010144341; WO2010144344; WO201065799; WO201065800; WO201065801; WO201065802; WO201037081; WO2009152079; WO2009151383; US20100311648; US20100280079; WO201081666; WO201034500; WO200910299; WO2008116665; WO201052256; WO201052255; WO201126015; US20100120783; WO201096854; US20100190793; WO201025142; WO2014144260; WO2017059075; and WO201015972. Further examples of MC4R agonists are found in U.S. Pat. No. 8,263,608; U.S. Pat. No. 8,247,530; U.S. Pat. No. 8,114,844; and U.S. Pat. No. 7,968,548. The entire teachings of these publications are incorporated herein by reference.

In some embodiments, the MC4R agonist is a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a pharmaceutically

acceptable salt thereof as described herein. In some embodiments, the MC4R agonist is a compound of any one of Formulas (I) or (II), or a pharmaceutically acceptable salt thereof as described herein. In one embodiment, the MC4R agonist is a compound of Formula (I). In one embodiment, the MC4R agonist is a compound of Formula (II).

- 5 In one example embodiment, the agonist of MC4R is a tripeptide D-Phe-Arg-Trp (SEQ ID NO: 560) or a pharmaceutical salt thereof. In another example, the agonist is any peptide that includes SEQ ID NO: 560 or a pharmaceutical salt thereof. In yet another example, the MC4R agonist is an acetylated tripeptide Ac-D-Phe-Arg-Trp-NH₂ (SEQ ID NO: 561) or a pharmaceutical salt thereof.
- 10 In some embodiments, the MC4R agonist is a compound of Formula (I):
- $$(R^2R^3)-A^1-C(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-A^{10}-R^1 \quad (I)$$
- or a pharmaceutically acceptable salt thereof, wherein A¹ is Acc, HN—(CH₂)_m—C(O), L- or D-amino acid, or deleted; A² is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu; A³ is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted; A⁴ is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X¹, X², X³, X⁴, X⁵)Phe; A⁵ is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X¹, X², X³, X⁴, X⁵)Phe, L-Phe or D-(Et)Tyr; A⁶ is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH((CH₂)_n-N(R⁴R⁵))-C(O); A⁷ is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip; A⁸ is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-(CH₂)_s-C(O), or deleted; A⁹ is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys; A¹⁰ is Acc, HN-(CH₂)_t-C(O), L- or D-amino acid, or deleted; R¹ is OH or NH₂; each of R² and R³ is, independently for each occurrence, selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₁-C₃₀)heteroalkyl, (C₁-C₃₀)acyl, (C₂-C₃₀)alkenyl, (C₂-C₃₀)alkynyl, aryl(C₁-C₃₀)alkyl, aryl(C₁-C₃₀)acyl, substituted (C₁-C₃₀)alkyl, substituted (C₁-C₃₀)heteroalkyl, substituted (C₁-C₃₀)acyl, substituted (C₂-C₃₀)alkenyl, substituted (C₂-C₃₀)alkynyl, substituted aryl(C₁-C₃₀)alkyl, and substituted aryl(C₁-C₃₀)acyl; each of R⁴ and R⁵ is, independently for each occurrence, H, (C₁-C₄₀)alkyl, (C₁-C₄₀)heteroalkyl, (C₁-C₄₀)acyl, (C₂-C₄₀)alkenyl, (C₂-C₄₀)alkynyl, aryl(C₁-C₄₀)alkyl, aryl(C₁-C₄₀)acyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl, substituted (C₁-C₄₀)acyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl, substituted aryl(C₁-C₄₀)alkyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl, or -C(NH)-NH₂; m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; n is, independently for each occurrence, 1, 2, 3, 4 or 5; s is, independently for each

occurrence, 1, 2, 3, 4, 5, 6, or 7; t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7; X', X², X³, X⁴, and X⁵ each is, independently for each occurrence, H, F, Cl, Br, I, -(C₁-C₁₀) alkyl, substituted (C₁-C₁₀) alkyl, (C₂-C₁₀) alkenyl, substituted (C₂-C₁₀) alkenyl, (C₂-C₁₀) alkynyl, substituted (C₂-C₁₀) alkynyl, aryl, substituted aryl, OH, NH₂, NO₂, or CN.

5 In some embodiments, for Formula (I), when R⁴ is (C₁-C₄₀)acyl, aryl(C₁-C₄₀)acyl, substituted (C₁-C₄₀)acyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl, or -C(NH)-NH₂, then R⁵ is H or (C₁-C₄₀)alkyl, (C₁-C₄₀)heteroalkyl, (C₂-C₄₀)alkenyl, (C₂-C₄₀)alkynyl, aryl(C₁-C₄₀)alkyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl, or substituted aryl(C₁-C₄₀)alkyl.

10 In some embodiments, for Formula (I), when R² is (C₁-C₃₀)acyl, aryl(C₁-C₃₀)acyl, substituted (C₁-C₃₀)acyl, or substituted aryl(C₁-C₃₀)acyl, then R³ is H, (C₁-C₃₀)alkyl, (C₁-C₃₀)heteroalkyl, (C₂-C₃₀)alkenyl, (C₂-C₃₀)alkynyl, aryl(C₁-C₃₀)alkyl, substituted (C₁-C₃₀)alkyl, substituted (C₁-C₃₀)heteroalkyl, substituted (C₂-C₃₀)alkenyl, substituted (C₂-C₃₀)alkynyl, or substituted aryl(C₁-C₃₀)alkyl;

15 In some embodiments, for Formula (I), either A³ or A⁸ or both must be present in said compound.

In some embodiments, for Formula (I) when A² is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen, then A⁹ is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen.

20 In some embodiments, for Formula (I), when A² is Asp or Glu, then A⁹ is Dab, Dap, Orn, or Lys.

In some embodiments, for Formula (I), when A⁸ is Ala or Gly, then A¹ is not Nle.

In some embodiments, for Formula (I), when A¹ is deleted, then R² and R³ cannot both be H.

25 In some embodiments, for Formula (I): A¹ is A6c, Arg, D-Arg, Cha, D-Cha, hCha, Chg, D-Chg, Gaba, Ile, Leu, hLeu, Met, β-hMet, 2-Nal, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, Val, or deleted; A² is Asp, Cys, D-Cys, hCys, D-hCys, Glu, Pen, or D-Pen; A³ is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, D-Glu, Gly, D-Ile, D-Leu, D-Tle, D-Val, or deleted; A⁴ is His or 3-Pal; A⁵ is D-Bal, D-1-Nal, D-2-Nal, D-Phe, D-Trp, or D-(Et)Tyr; A⁶ is Arg, or hArg; A⁷ is Bal, Bip, 1-Nal, 2-Nal, Trp, D-Trp; A⁸ is A6c, D-Ala, Aha, Ahx, Ala, β-Ala, Apn, Gaba, Gly or deleted; A⁹ is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen; and A¹⁰ is Thr, or deleted, wherein at least one of A³ or A⁸ is deleted, but not both.

30

In some embodiments, the compound of Formula (I) is a compound disclosed in International Patent Application Publication Number WO 2007/008704, which is incorporated herein by reference in its entirety.

In some embodiments, the compound of Formula (I) is selected from:

- 5 (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp- β -Ala-Lys)-NH₂;
- (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH₂;
- (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH₂;
- (SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH₂;
- (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp- β -Ala-D-Cys)-Thr-NH₂;
- 10 (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH₂;
- (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;
- (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH₂;
- (SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- 15 (SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 14) Ac-Nle-c(Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
- 20 (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 20) Ac-Nle-c(D-Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- 25 (SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
- (SEQ ID NO: 25) Ac-Nle-c(Cys- β -Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
- 30 (SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
- (SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;

- (SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
5 (SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
10 (SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
15 (SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 45) n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 46) n-butyryl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
20 (SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
25 (SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH₂;
30 (SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH₂;

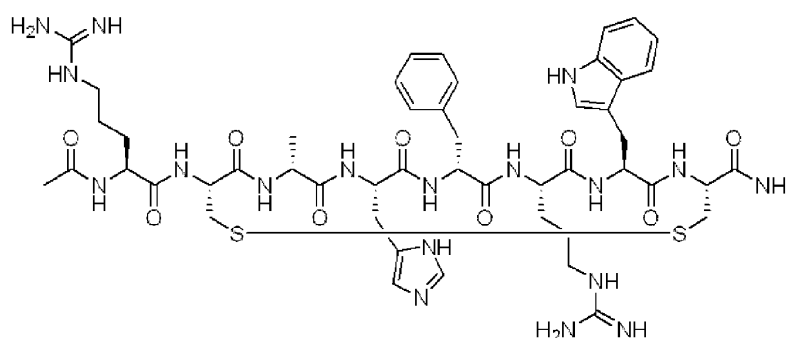
- (SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH₂;
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH₂;
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH₂;
5 (SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH₂;
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH₂;
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH₂;
10 (SEQ ID NO: 68) n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 69) n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH₂;
15 (SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH₂;
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
20 (SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;
(SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;
(SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH₂;
(SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;
25 (SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂;
(SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂;
(SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH₂;
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH₂;
30 (SEQ ID NO: 88) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH₂;

- (SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH₂;
5 (SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
(SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
10 (SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
15 (SEQ ID NO: 104) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 107) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;
(SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
20 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH₂;
(SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH₂;
(SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
25 (SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 115) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH;
(SEQ ID NO: 116) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH;
(SEQ ID NO: 117) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH;
(SEQ ID NO: 118) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH;
30 (SEQ ID NO: 119) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH;
(SEQ ID NO: 120) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH;

- (SEQ ID NO: 121) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH;
 (SEQ ID NO: 122) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
 (SEQ ID NO: 123) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
 (SEQ ID NO: 124) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
 5 (SEQ ID NO: 125) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
 (SEQ ID NO: 126) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
 (SEQ ID NO: 127) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
 (SEQ ID NO: 128) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;
 (SEQ ID NO: 129) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH;
 10 (SEQ ID NO: 130) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH;
 (SEQ ID NO: 131) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH;
 (SEQ ID NO: 132) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH;
 (SEQ ID NO: 133) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH;
 (SEQ ID NO: 134) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH;
 15 (SEQ ID NO: 135) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH;
 (SEQ ID NO: 136) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH;
 (SEQ ID NO: 137) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;
 (SEQ ID NO: 138) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH;
 (SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
 20 (SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 25 (SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂; and
 (SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂,

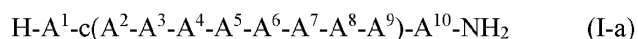
or a pharmaceutically acceptable salt thereof. In embodiments, the compound of Formula (I) is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140) or a
 30 pharmaceutically acceptable salt thereof. Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140), also known as RM-493 and setmelanotide, is a peptide that retains

the specificity and functionality of the naturally occurring hormone that activates MC4R and has not been shown to adversely affect blood pressure in clinical trials (see, e.g., Chen et al. *J. Clin. Endocrinol. Metab.* 2015;100(4):1639-45. The structure of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140) is shown below:



5

In some embodiments, the MC4R agonist is a compound of Formula (I-a):



or a pharmaceutically acceptable salt thereof, wherein:

A¹ is Phe, D-Phe, or Nle;

10 A² is Cys;

A³ is deleted;

A⁴ is His;

A⁵ is D-Phe or D-(Et)Tyr;

A⁶ is Arg or hArg;

15 A⁷ is Trp or Bip;

A⁸ is Ala, β-Ala, Gaba, or Apn;

A⁹ is D-Cys; and

A¹⁰ is Thr or deleted.

In some embodiments, the compound of Formula (I-a) is selected from:

20 (SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;

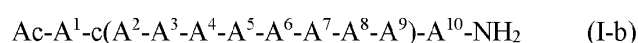
(SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH₂;

(SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;

- (SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂;
 5 (SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂; and
 (SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂.

In some embodiments, the MC4R agonist is a compound of Formula (I-b):



- 10 or a pharmaceutically acceptable salt thereof, wherein:

A¹ is Nle, A6c, D-2-Nal, Cha, Oic, Chg, hCha, D-Cha, D-hCha, Nip, hPro, hLeu, Phe, D-Phe, D-Chg, hPhe, β-hMet, Gaba, Leu, Ile, Val, 2-Nal, Arg or D-Arg;

A² is Asp, Cys, D-Cys, or Pen;

A³ is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, D-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha,

- 15 deleted;

A⁴ His or 3-Pal;

A⁵ is Phe, D-Phe, or D-2-Nal;

A⁶ is Arg;

A⁷ is Trp, 1-Nal, 2-Nal, Bal, or D-Trp;

- 20 A⁸ is β-Ala, A6c, Ahx, Apn, Gaba, Ala, Aha, D-Ala or deleted;

A⁹ is Lys, Cys, D-Cys, or Pen;

A¹⁰ is deleted.

wherein A² and A⁹ are pairwise selected to form a disulfide or lactam bridge.

- 25 In some embodiments, the compound of Formula (I-b) is selected from:

(SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH₂;

(SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH₂;

(SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH₂;

(SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;

- 30 (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH₂;

(SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;

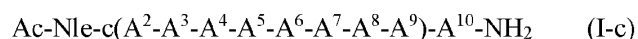
- (SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
5 (SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
10 (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
15 (SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
20 (SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
25 (SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
30 (SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;

- (SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
5 (SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
10 (SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH₂;
15 (SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH₂;
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH₂;
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH₂;
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
20 (SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH₂;
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH₂;
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH₂;
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH₂;
25 (SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH₂;
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
30 (SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH₂;

- (SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH₂;
5 (SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH₂;
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH₂;
10 (SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
15 (SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
20 (SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH₂;
25 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH₂;
(SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
30 (SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;

- (SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 5 (SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂; and
 (SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂.

In some embodiments, the MC4R agonist is a compound of Formula (I-c):



or a pharmaceutically acceptable salt thereof, wherein:

- 10 A² is Asp, Cys, D-Cys, or Pen;
 A³ is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, Aib, Dl-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle,
 D-Cha, or deleted;
 A⁴ is His or 3-Pal;
 A⁵ is D-Phe, D-2-Nal, or Phe;
 15 A⁶ is Arg;
 A⁷ is Trp, D-Trp, 2-Nal, 1-Nal, Bal;
 A⁸ is β-Ala, A6c, Ahx, Apn, Gaba, D-Ala, Aha, Ala or deleted;
 A⁹ is Lys, Cys, D-Cys or Pen; and
 A¹⁰ is deleted,
 20 wherein A² and A⁹ are pairwise selected to form a disulfide or lactam bridge.

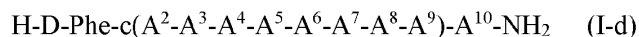
In some embodiments, the compound of Formula (I-c) is selected from:

- (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH₂;
 (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH₂;
 25 (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH₂;
 (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;
 (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH₂;
 (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
 (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 30 (SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;

- (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
5 (SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
10 (SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
15 (SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH₂;
20 (SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH₂;
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH₂;
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH₂;
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH₂;
25 (SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH₂;
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH₂;
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH₂;
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
30 (SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH₂;

- (SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH₂;
 (SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH₂;
 (SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH₂;
 (SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 5 (SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH₂;
 (SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH₂;
 (SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 10 (SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH₂;
 (SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH₂;
 (SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH₂;
 15 (SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 20 (SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH₂;
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH₂;
 25 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH₂; and
 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH₂.

In some embodiments, the MC4R agonist is a compound of Formula (I-d):



or a pharmaceutically acceptable salt thereof, wherein:

- 30 A² is Cys;
 A³ is deleted;

A⁴ is His;

A⁵ is D-Phe or D-(Et)Tyr;

A⁶ is Arg or hArg;

A⁷ is Trp or Bip;

5 A⁸ is Ala, β-Ala, or Gaba;

A⁹ is D-Cys; and

A¹⁰ is Thr.

In some embodiments, the compound of Formula (I-d) is selected from:

(SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH₂;

10 (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH₂;

(SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;

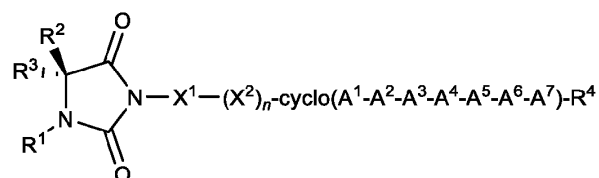
(SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH₂;

15 (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂; and

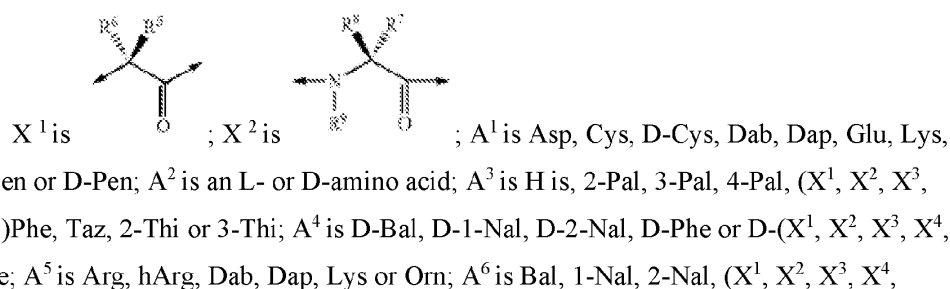
(SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂.

In some embodiments, the MC4R agonist is a compound of Formula (II):



20

or a pharmaceutically acceptable salt thereof, wherein:



X⁵)Phe or Trp; A⁷ is Asp, Cys, D-Cys, Dab, Dap, Glu, Lys, Orn, Pen or D-Pen; R¹ is H, (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)alkyl; R² and R³ each is, independently, H, (C₁-C₁₀)alkyl, (C₁-C₁₀)heteroalkyl, aryl(C₁-C₅)alkyl, substituted (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)heteroalkyl or substituted aryl(C₁-C₅)alkyl or R² and R³ may be fused together form a cyclic moiety; R⁴ is OH, NH₂, CO₂H or C(O)NH₂; R⁵ and R⁶ each is, independently, H, (C₁-C₁₀)alkyl, (C₁-C₁₀)heteroalkyl, aryl(C₁-C₅)alkyl, substituted (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)heteroalkyl or substituted aryl(C₁-C₅)alkyl or R⁵ and R⁶ may be fused together form a cyclic moiety; R⁷ and R⁸ each is, independently, H, (C₁-C₁₀)alkyl, (C₁-C₁₀)heteroalkyl, aryl(C₁-C₅)alkyl, substituted (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)heteroalkyl or substituted aryl(C₁-C₅)alkyl; or R⁷ and R⁸ may be fused together form a cyclic moiety; R⁹ is H, (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)alkyl; and n is, independently for each occurrence thereof, 0, 1, 2, 3, 4, 5, 6 or 7; or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula (II), A¹ is Cys; A² is D-Ala, Asn, Asp, Gln, Glu or D-Phe; A³ is H is; A⁴ is D-2-Nal or D-Phe; A⁵ is Arg; A⁶ is Trp; and A⁷ is Cys or Pen; each of R', R², R³, and R⁹ is, independently, H; R⁴ is C(O)NH₂; each of R⁵ and R⁶ is, independently, H, (C₁-C₁₀)heteroalkyl, substituted (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)heteroalkyl or R⁵ and R⁶ may be fused together form a cyclic moiety; and each of R⁷ and R⁸ is, independently, H, (C₁-C₁₀)alkyl, (C₁-C₁₀)heteroalkyl, substituted (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)heteroalkyl; or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula (II) is selected from:
 (SEQ ID NO: 148) Hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 149) Hydantoin(C(O)-(Nle-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 150) Hydantoin(C(O)-(Gly-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 151) Hydantoin(C(O)-(Nle-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 152) Hydantoin(C(O)-(Gly-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 153) Hydantoin(C(O)-(Nle-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 154) Hydantoin(C(O)-(Gly-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 155) Hydantoin(C(O)-(Ala-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 156) Hydantoin(C(O)-(D-Ala-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;

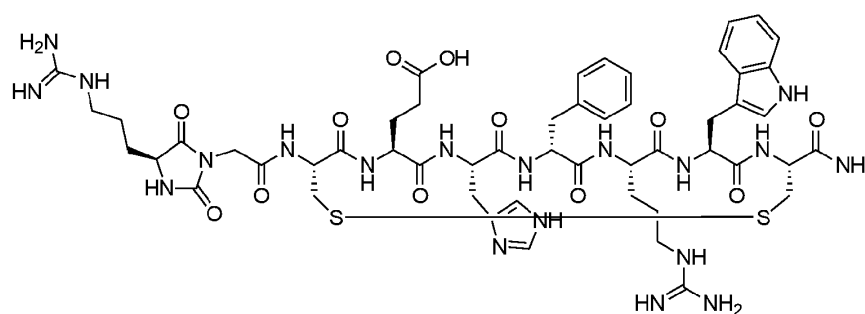
- (SEQ ID NO: 157) Hydantoin(C(O)-(Aib-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 158) Hydantoin(C(O)-(Val-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 159) Hydantoin(C(O)-(Ile-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 160) Hydantoin(C(O)-(Leu-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-
5 NH₂;
(SEQ ID NO: 161) Hydantoin(C(O)-(Gly-Gly))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 162) Hydantoin(C(O)-(Nle-Gly))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 163) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-
NH₂;
10 (SEQ ID NO: 164) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-
NH₂;
(SEQ ID NO: 165) Hydantoin(C(O)-(Arg-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-
NH₂;
(SEQ ID NO: 166) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-
15 NH₂;
(SEQ ID NO: 167) Hydantoin(C(O)-(Arg-Gly))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-
NH₂;
(SEQ ID NO: 168) Hydantoin(C(O)-(Ala-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 169) Hydantoin(C(O)-(Val-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
20 (SEQ ID NO: 170) Hydantoin(C(O)-(Gly-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 171) Hydantoin(C(O)-(A6c-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-
NH₂;
(SEQ ID NO: 172) Hydantoin(C(O)-(Gly-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 173) Hydantoin(C(O)-(Ala-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
25 (SEQ ID NO: 174) Hydantoin(C(O)-(D-Ala-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-
NH₂;
(SEQ ID NO: 175) Hydantoin(C(O)-(Val-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 176) Hydantoin(C(O)-(Leu-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 177) Hydantoin(C(O)-(Cha-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-
30 NH₂;
(SEQ ID NO: 178) Hydantoin(C(O)-(Aib-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;

- (SEQ ID NO: 179) Hydantoin(C(O)-(Gly-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 180) Hydantoin(C(O)-(Gly-Arg))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 181) Hydantoin(C(O)-(Gly-Arg))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 5 (SEQ ID NO: 182) Hydantoin(C(O)-(Gly-Arg))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 183) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 184) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 10 (SEQ ID NO: 185) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂; and
 (SEQ ID NO: 186) Hydantoin(C(O)-(Nle-Ala))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂,
 or a pharmaceutically acceptable salt thereof.

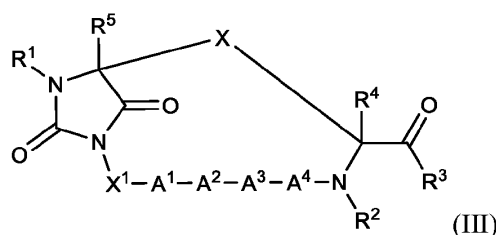
15

In some embodiments, the compound of Formula (II) is described in WO2008/147556 or International Patent Application Number PCT/US08/06675, each of which is incorporated herein by reference in its entirety.

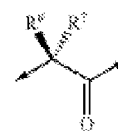
- In embodiments, the compound of Formula (II) is hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 148) or a pharmaceutically acceptable salt thereof, also known as RM-511. The structure of hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 148) is shown below:



In some embodiments, the MC4R agonist is a compound of Formula (III):

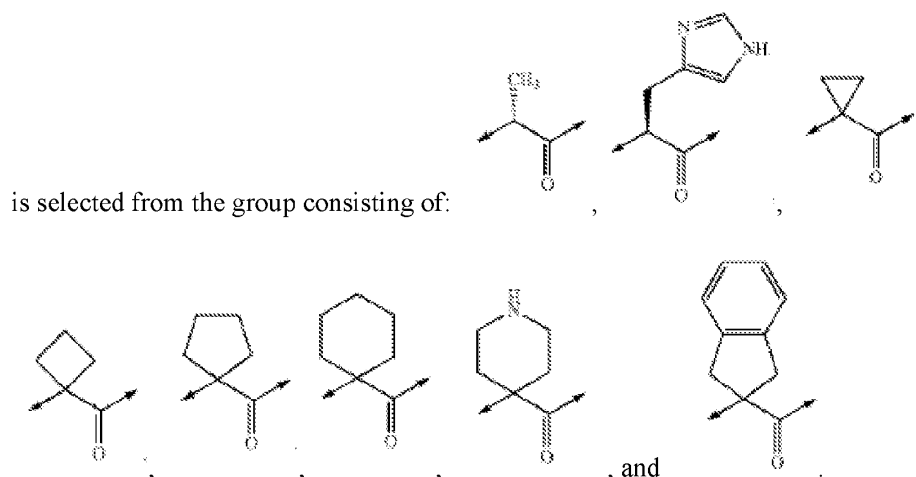


or a pharmaceutically acceptable salt thereof, wherein X is selected from the group consisting of -CH₂-S-S-CH₂-, -C(CH₃)₂-S-S-CH₂-, -CH₂-S-S-C(CH₃)₂-, -C(CH₃)₂-S-S-C(CH₃)₂-, -
 (CH₂)₂-S-S-CH₂-, -CH₂-S-S-(CH₂)₂-, -(CH₂)₂-S-S-(CH₂)₂-, -C(CH₃)₂-S-S-(CH₂)₂-, -(CH₂)₂-S-
 5 S-C(CH₃)₂-, -(CH₂)_r-C(O)-NR⁸-(CH₂)_r-and -(CH₂)_r-NR⁸-C(O)-(CH₂)_t-; R² each is,
 independently, H, (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)alkyl; R³ is -OH or -NH₂; R⁴ and R⁵



each is, independently, H, (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)alkyl; X¹ is ; A¹ is
 H is, 2-Pal, 3-Pal, 4-Pal, (X¹, X², X³, X⁴, X⁵)Phe, Taz, 2-Thi, 3-Thi or is deleted;
 A² is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-(X¹, X², X³, X⁴, X⁵)Phe; A³ is Arg, hArg, Dab,
 10 Dap, Lys or Orn; A⁴ is Bal, 1-Nal, 2-Nal, (X¹, X², X³, X⁴, X⁵)Phe or Trp; R⁶ and R⁷ each is,
 independently for each occurrence thereof, H, (C₁-C₁₀)heteroalkyl, aryl(C₁-C₅)alkyl,
 substituted (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)heteroalkyl or substituted aryl(C₁-C₅)alkyl
 provided that R⁶ and R⁷ may be joined together to form a ring; R⁸ is H, (C₁-C₁₀)alkyl or
 substituted (C₁-C₁₀)alkyl; r is, independently for each occurrence thereof, 1, 2, 3, 4 or 5; and t
 15 is, independently for each occurrence thereof, 1 or 2.

Compounds according to the foregoing formula can include compounds wherein X¹



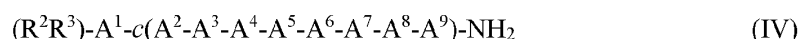
Compounds of Formula (III) are disclosed in International Patent Publication WO
 5 2008/147556 or International Patent Application Number PCT/US08/06675, each of which is
 incorporated herein by reference in its entirety.

In some embodiments, the compound of Formula (III) is selected from:

- (SEQ ID NO: 187) c[Hydantoin(C(O)-(Cys-D-Ala))-His-D-Phe-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 188) c[Hydantoin(C(O)-(hCys-D-Ala))-His-D-Phe-Arg-Trp-Cys]-NH₂;
 10 (SEQ ID NO: 189) c[Hydantoin(C(O)-(Cys-D-Ala))-His-D-2-Nal-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 190) c[Hydantoin(C(O)-(hCys-D-Ala))-His-D-2-Nal-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 191) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 192) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Orn]-NH₂;
 (SEQ ID NO: 193) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Dab]-NH₂;
 15 (SEQ ID NO: 194) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Dap]-NH₂;
 (SEQ ID NO: 195) c[Hydantoin(C(O)-(Asp-His))-D-2-Nal-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 196) c[Hydantoin(C(O)-(Asp-His))-D-Phe-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 197) c[Hydantoin(C(O)-(Asp-A3c))-D-Phe-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 198) c[Hydantoin(C(O)-(Asp-A5c))-D-Phe-Arg-Trp-Lys]-NH₂;
 20 (SEQ ID NO: 199) c[Hydantoin(C(O)-(Asp-A6c))-D-Phe-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 200) c[Hydantoin(C(O)-(Asp-A3c))-D-2-Nal-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 201) c[Hydantoin(C(O)-(Asp-A5c))-D-2-Nal-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 202) c[Hydantoin(C(O)-(Asp-A6c))-D-2-Nal-Arg-Trp-Lys]-NH₂;

- (SEQ ID NO: 203) c[Hydantoin(C(O)-(Asp-Aic))-D-Phe-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 204) c[Hydantoin(C(O)-(Asp-Apc))-D-Phe-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 205) c[Hydantoin(C(O)-(Asp-Aic))-D-2-Nal-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 206) c[Hydantoin(C(O)-(Asp-Apc))-D-2-Nal-Arg-Trp-Lys]-NH₂;
 5 (SEQ ID NO: 207) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Orn]-NH₂;
 (SEQ ID NO: 208) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Dab]-NH₂;
 (SEQ ID NO: 209) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Dap]-NH₂;
 (SEQ ID NO: 210) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Lys]-NH₂;
 (SEQ ID NO: 211) c[Hydantoin(C(O)-(Glu-His))-D-Phe-Arg-Trp-Dap]-NH₂; and
 10 (SEQ ID NO: 212) c[Hydantoin(C(O)-(Glu-His))-D-Phe-Arg-Trp-Lys]-NH₂,
 or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is a compound of Formula (IV):



- 15 or a pharmaceutically acceptable salt thereof, wherein A¹ is Nle or deleted; A² is Cys or Asp;
 A³ is Glu or D-Ala; A⁴ is His; A⁵ is D-Phe; A⁶ is Arg; A⁷ is Trp, 2-Nal or Bal; A⁸ is Gly, Ala,
 D-Ala, 3-Ala, Gaba or Apn; A⁹ is Cys or Lys; each of R² and R³ is independently selected
 from the group consisting of H or (C₁-C₆)acyl.

- In exemplary embodiments of Formula (IV): (I) when R² is (C₁-C₆)acyl, then R³ is H;
 20 and (II) when A² is Cys, then A⁹ is Cys.

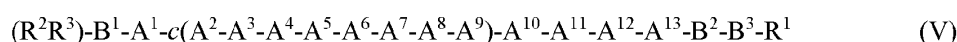
Exemplary MC4R agonists of Formula (IV) are disclosed in International Patent
 Application Publication Number WO 2007/008704, which is incorporated herein by
 reference in its entirety.

In some embodiments, the compound of Formula (IV) is selected from:

- 25 (SEQ ID NO: 213) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH₂;
 (SEQ ID NO: 214) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH₂;
 (SEQ ID NO: 215) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH₂;
 (SEQ ID NO: 216) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 217) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;
 30 (SEQ ID NO: 218) Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH₂;
 (SEQ ID NO: 219) Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH₂;

(SEQ ID NO: 220) Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH₂;
 (SEQ ID NO: 221) Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH₂;
 (SEQ ID NO: 222) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH₂; and
 (SEQ ID NO: 223) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH₂,
 5 or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is a compound of Formula (V):



or a pharmaceutically acceptable salt thereof. B¹ is a peptide moiety which contains 5, 6, 7, 8,
 10 9, 10, 11, 12, 13, 14, or 15 amino acids, wherein at least 5 amino acids are independently
 selected from the group consisting of L-Arg, D-Arg, L-hArg and D-hArg, or B¹ is optionally
 deleted; A¹ is Acc, HN-(CH₂)_m-C(O), L- or D-amino acid or deleted; A² is Cys, D-Cys, hCys,
 D-hCys, Pen, D-Pen, Asp or Glu; A³ is Gly, Glu, Ala, β-Ala, Gaba, Aib, D-amino acid or
 deleted; A⁴ is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi or (X', X², X³, X⁴, X⁵)Phe; A⁵ is D-
 15 Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X¹, X², X³, X⁴, X⁵)Phe, D-(Et)Tyr, D-Dip, D-Bip
 or D-Bpa; A⁶ is Arg, hArg, Dab, Dap, Lys, Orn or HN-CH((CH₂)_n-N(R⁴R⁵))-C(O); A⁷ is Trp,
 1-Nal, 2-Nal, Bal, Bip, Dip, Bpa, D-Trp, D-1-Nal, D-2-Nal, D-Bal, D-Bip, D-Dip or D-Bpa;
 A⁸ is Gly, D-Ala, Acc, Ala, β-Ala, Gaba, Apn, Ahx, Aha, HN-(CH₂)_s-C(O) or deleted; A⁹ is
 Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn or Lys; A¹⁰ is Acc, HN-(CH₂)_r-C(O),
 20 Pro, hPro, 3-Hyp, 4-Hyp, Thr, an L- or D-amino acid or deleted; A¹¹ is Pro, hPro, 3-Hyp, 4-
 Hyp or deleted; A¹² is Lys, Dab, Dap, Arg, hArg or deleted; A¹³ is Asp, Glu or deleted; B² is
 a peptide moiety containing 1, 2, 3, 4, or 5 amino acids or deleted, B³ is a peptide moiety
 which contains 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids wherein at least 5 amino
 acids are independently selected from the group consisting of L-Arg, D-Arg, L-hArg and D-
 25 hArg, or is deleted; R¹ is OH or NH₂; R² and R³ each is, independently for each occurrence,
 selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₁-C₃₀)heteroalkyl, (C₁-C₃₀)acyl,
 (C₂-C₃₀)alkenyl, (C₂-C₃₀)alkynyl, aryl(C₁-C₃₀)alkyl, aryl(C₁-C₃₀)acyl, substituted (C₁-
 C₃₀)alkyl, substituted (C₁-C₃₀)heteroalkyl, substituted (C₁-C₃₀)acyl, substituted (C₂-
 C₃₀)alkenyl, substituted (C₂-C₃₀)alkynyl, substituted aryl(C₁-C₃₀)alkyl and substituted
 30 aryl(C₁-C₃₀)acyl; R⁴ and R⁵ each is, independently for each occurrence, H, (C₁-C₄₀)alkyl, (C₁-
 C₄₀)heteroalkyl, (C₁-C₄₀)acyl, (C₂-C₄₀)alkenyl, (C₂-C₄₀)alkynyl, aryl(C₁-C₄₀)alkyl, aryl(C₁-

- C₄₀)acyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl, substituted (C₁-C₄₀)acyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl, substituted aryl(C₁-C₄₀)alkyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl or C(NH)-NH₂; n is, independently for each occurrence, 1, 2, 3, 4 or 5; m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; s is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; t is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; X¹, X², X³, X⁴ and X⁵ each is, independently for each occurrence, H, F, Cl, Br, I, -(C₁-C₁₀) alkyl, substituted (C₁-C₁₀) alkyl, (C₂-C₁₀) alkenyl, substituted (C₂-C₁₀) alkenyl, (C₂-C₁₀) alkynyl, substituted (C₂-C₁₀) alkynyl, aryl, substituted aryl, OH, NH₂, NO₂ or CN.
- 10 In some embodiments of Formula (V):
- (I) when R¹ is (C₁-C₄₀)acyl, aryl(C₁-C₄₀)acyl, substituted (C₁-C₄₀)acyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl or C(NH)—NH₂, then R⁵ is H, (C₁-C₄₀)alkyl, (C₁-C₄₀)heteroalkyl, (C₂-C₄₀)alkenyl, (C₂-C₄₀)alkynyl, aryl(C₁-C₄₀)alkyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl or substituted aryl(C₁-C₄₀)alkyl;
- 15 (II) when R² is (C₁-C₃₀)acyl, aryl(C₁-C₃₀)acyl, substituted (C₁-C₃₀)acyl or substituted aryl (C₁-C₃₀)acyl, then R³ is H, (C₁-C₃₀)alkyl, (C₁-C₃₀)heteroalkyl, (C₂-C₃₀)alkenyl, (C₂-C₃₀)alkynyl, aryl(C₁-C₃₀)alkyl, substituted (C₁-C₃₀)alkyl, substituted (C₁-C₃₀)heteroalkyl, substituted (C₂-C₃₀)alkenyl, substituted (C₂-C₃₀)alkynyl or substituted aryl(C₁-C₃₀)alkyl;
- 20 (III) neither B¹ nor B² contains one or more of the following amino acid sequences: Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃, Tyr-Ala-Arg-Lys-Ala-(Arg)₂-Gln-Ala-(Arg)₂, Tyr-Ala-Arg-(Ala)₂-(Arg)₂-(Ala)₂-(Arg)₂, Tyr-Ala-(Arg)₉, Tyr-(Ala)₃-(Arg)₇, Tyr-Ala-Arg-Ala-Pro-(Arg)₂-Ala-(Arg)₃ or Tyr-Ala-Arg-Ala-Pro-(Arg)₂-Pro-(Arg)₂;
- (IV) either B¹ or B² or both must be present in said compound;
- 25 (V) when A² is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen, then A⁹ is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen; and
- (VI) when A² is Asp or Glu, then A⁹ is Dab, Dap, Orn or Lys.
- In some embodiments of Formula (V):
- B¹ is Arg-Lys-Gln-Lys-(Arg)₅, Arg-(Lys)₂-Arg-Gln-(Arg)₄, Arg-(Lys)₂-(Arg)₃-Gln-(Arg)₂, Arg-(Lys)₂-(Arg)₄-Gln-Arg, Arg-(Lys)₂-(Arg)₅-Gln, Arg-(Lys)₂-Gln-(Arg)₅, Arg-Gln-(Lys)₂-(Arg)₅, Arg-Gln-(Arg)₇, Arg-Gln-(Arg)₈, (Arg)₂-Gln-(Arg)₆, (Arg)₂-Gln-(Arg)₇,
- 30

(Arg)₃-Gln-(Arg)₅, (Arg)₃-Gln-(Arg)₆, (Arg)₄-Gln-(Arg)₄, (Arg)₄-Gln-(Arg)₅, (Arg)₅, (Arg)₅-Gln-(Arg)₃, (Arg)₅-Gln-(Arg)₄, (Arg)₆, (Arg)₆-Gln-(Arg)₃, (Arg)₇, (Arg)₇-Gln-(Arg)₂, (Arg)₈, (Arg)₈-Gln-Arg, (Arg)₉, (Arg)₉-Gln, (D-Arg)₅, (D-Arg)₆, (D-Arg)₇, (D-Arg)₈, (D-Arg)₉, Gln-Arg-(Lys)₂-(Arg)₅, Gln-(Arg)₈, Gln-(Arg)₉, Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃, Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-Doc; or deleted;

B² is β-Ala, β-Ala-Gly, β-Ala-Tyr, β-Ala-Tyr-Gly, (β-Ala)₂, (β-Ala)₂-Gly, (β-Ala)₂-Tyr, (β-Ala)₂-Tyr-Gly, Doc, Doc-Gly, Doc-Tyr, Doc-Tyr-Gly, (Doc)₂, (Doc)₂-Gly, (Doc)₂-Tyr, (Doc)₂-Tyr-Gly, or deleted;

B³ is Arg-Lys-Gln-Lys-(Arg)₅, Arg-Lys-(Arg)₃-Gln-(Arg)₃, Arg-(Lys)₂-Arg-Gln-(Arg)₄, Arg-(Lys)₂-Gln-(Arg)₅, Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃, Arg-(Lys)₂-(Arg)₃-Gln-(Arg)₂, Arg-(Lys)₂-(Arg)₄-Gln-Arg, Arg-(Lys)₂-(Arg)₅-Gln, Arg-Gln-(Lys)₂-(Arg)₅, Arg-Gln-(Arg)₇, Arg-Gln-(Arg)₈, (Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃, (Arg)₂-Gln-(Arg)₆, (Arg)₂-Gln-(Arg)₇, (Arg)₃-Gln-(Arg)₅, (Arg)₃-Gln-(Arg)₆, (Arg)₄-Gln-(Arg)₄, (Arg)₄-Gln-(Arg)₅, (Arg)₅, (Arg)₅-Gln-(Arg)₃, (Arg)₅-Gln-(Arg)₄, (Arg)₆, (Arg)₆-Gln-(Arg)₃, (Arg)₇, (Arg)₇-Gln-(Arg)₂, (Arg)₈, (Arg)₈-Gln-Arg, (Arg)₉, (Arg)₉-Gln, (D-Arg)₅, (D-Arg)₆, (D-Arg)₇, (D-Arg)₈, (D-Arg)₉, Gln-Arg-(Lys)₂-(Arg)₅, Gln-(Arg)₈, Gln-(Arg)₉, or deleted;

A¹ is A6c, Cha, hCha, Chg, D-Chg, hChg, Gaba, hLeu, Met, β-hMet, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, or deleted;

A² is Cys;

A³ is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, Glu, Gly, D-Ile, D-Leu, D-Met, D-Nle, D-Phe, D-Tle, D-Trp, D-Tyr, D-Val, or deleted;

A⁴ is H;

A⁵ is D-Bal, D-1-Nal, D-2-Nal, D-Phe, D-(X¹, X², X³, X⁴, X⁵)Phe, D-Trp, or D-(Et)Tyr;

A⁶ is Arg or hArg;

A⁷ is Bal, Bip, 1-Nal, 2-Nal, Trp, or D-Trp;

A⁸ is A5c, A6c, Aha, Ahx, Ala, β-Ala, Apn, Gaba, Gly, or deleted;

A⁹ is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen;

A¹⁰ is Pro, Thr or deleted;

A¹¹ is Pro or deleted;

A¹² is Arg, Lys, or deleted;

A¹³ is Asp or deleted;

each of R² and R³ is, independently, H or acyl;

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula (V) is selected from:

- 5 (SEQ ID NO: 224) Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-NH₂;
- (SEQ ID NO: 225) Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-Doc-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-NH₂;
- (SEQ ID NO: 226) Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-β-Ala-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- 10 (SEQ ID NO: 227) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-β-Ala-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 228) Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Doc)₂-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 229) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Pro)₂-Lys-Asp-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 230) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys)-(Pro)₂-Lys-Asp-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 231) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(β-Ala)₂-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 232) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Pro)₂-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 233) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys)-(Pro)₂-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 234) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 235) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 236) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Doc)₂-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- 30 (SEQ ID NO: 237) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Doc)₂-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 237) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 238) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 239) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 240) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 241) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
- 10 Tyr-Gly-Arg-(Lys)₂-Arg-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 242) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)₂-Gln-(Arg)₅-NH₂;
- (SEQ ID NO: 243) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-Gln-Lys-(Arg)₅-NH₂;
- 15 (SEQ ID NO: 244) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)₂-(Arg)₄-Gln-Arg-NH₂;
- (SEQ ID NO: 245) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Aib-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 246) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-
- 20 (Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 247) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 248) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₆-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 249) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 250) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 251) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
- 30 (Arg)₆-Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 252) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-
(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 253) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-
(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 254) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 255) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
Tyr-Gly-Arg-(Lys)₂-(Arg)₃-Gln-(Arg)₂-NH₂;
- (SEQ ID NO: 256) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
10 Tyr-Gly-Arg-Gln-(Lys)₂-(Arg)₅-NH₂;
- (SEQ ID NO: 257) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
Tyr-Gly-Arg-(Lys)₂-(Arg)₅-Gln-NH₂;
- (SEQ ID NO: 258) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 259) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 260) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 261) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
20 Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 262) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 263) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
Tyr-Gly-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 264) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
Gly-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 265) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 266) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
30 Tyr-Gly-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 267) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 268) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Gly-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 269) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 270) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 271) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
- 10 Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 272) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 273) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 274) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 275) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 276) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
- 20 Tyr-Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 277) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Gly-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 278) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 279) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 280) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 281) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
- 30 Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 282) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 283) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- 5 (SEQ ID NO: 284) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 285) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 286) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 10 (SEQ ID NO: 287) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 288) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- 15 (SEQ ID NO: 289) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 290) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 291) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 292) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 293) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 25 (SEQ ID NO: 294) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 295) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 296) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-(Arg)₆-Gln-(Arg)₃-NH₂;
- 30

- (SEQ ID NO: 297) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 298) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Arg)₅-Gln-(Arg)₄-NH₂;
- 5 (SEQ ID NO: 299) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 300) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 301) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-
- 10 Tyr-Gly-(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 302) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 303) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 15 (SEQ ID NO: 304) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 305) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 306) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-
- 20 Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 307) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 308) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 25 (SEQ ID NO: 309) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 310) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-β-Ala-Tyr-Gly-(Arg)₆-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 311) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Arg-Asp-β-Ala-
- 30 Tyr-Gly-(Arg)₆-Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 312) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 313) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-Arg-(Lys)₂-Arg-Gln-(Arg)₄-NH₂;
- 5 (SEQ ID NO: 314) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-Arg-(Lys)₂-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 315) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 316) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)₅-Gln-
- 10 (Arg)₃-NH₂;
- (SEQ ID NO: 317) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 318) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 15 (SEQ ID NO: 319) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 320) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 321) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)₂-Lys-
- 20 (Arg)₂-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 322) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 323) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)₂-Lys-(Arg)₂-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 324) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Arg-Lys-(Arg)₃-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 325) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 326) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Gly-(Arg)₅-
- 30 Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 327) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅ - Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 328) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)₅-Gln-(Arg)₃ - NH₂;
- 5 (SEQ ID NO: 329) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 330) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)₅ - Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 331) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)₂ -(Arg)₅-Gln-
- 10 (Arg)₃-NH₂;
- (SEQ ID NO: 332) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)₂ -Gly-(Arg)₅ -Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 333) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)₂ -Tyr-Gly-(Arg)₅ - Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 334) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 335) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)₅ - Gln-(Arg)₄ -NH₂;
- (SEQ ID NO: 336) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-(Arg)₅-Gln-
- 20 (Arg)₄-NH₂;
- (SEQ ID NO: 337) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 338) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅ - Gln-(Arg)₄-NH₂;
- 25 (SEQ ID NO: 339) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)₅ -Gln-(Arg)₄ - NH₂;
- (SEQ ID NO: 340) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 341) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-
- 30 (Arg)₄-NH₂;

- (SEQ ID NO: 342) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 343) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 5 (SEQ ID NO: 344) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 345) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 346) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 10 (SEQ ID NO: 347) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 348) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 349) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 350) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 351) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 352) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 353) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)₂-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 354) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 355) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 356) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 30 (SEQ ID NO: 357) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 358) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 359) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)₂-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 360) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 361) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 362) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 10 (SEQ ID NO: 363) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 364) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 365) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)₂-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 15 (SEQ ID NO: 366) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 367) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 20 (SEQ ID NO: 368) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 369) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 370) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 25 (SEQ ID NO: 371) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)₂-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 372) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 373) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 30

- (SEQ ID NO: 374) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 375) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 376) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 377) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 378) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)₅-Gln-
- 10 (Arg)₃-NH₂;
- (SEQ ID NO: 379) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 380) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 381) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 382) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 383) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 384) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 385) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 386) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 387) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 388) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)₅-Gln-
- 30 (Arg)₃-NH₂;

- (SEQ ID NO: 389) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 390) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 391) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 392) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 393) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 10 (SEQ ID NO: 394) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 395) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 15 (SEQ ID NO: 396) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 397) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 398) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- 20 (SEQ ID NO: 399) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 400) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;
- 25 (SEQ ID NO: 401) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 402) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 403) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 30

- (SEQ ID NO: 404) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- β -Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 405) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- β -Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 406) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)- β -Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 407) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)- β -Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 408) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)- β -Ala-(Arg)₅-Gln-
- 10 (Arg)₃-NH₂;
- (SEQ ID NO: 409) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)- β -Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 410) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)- β -Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 411) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp- β -Ala-Cys)- β -Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 412) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp- β -Ala-Cys)- β -Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 413) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- β -Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 414) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- β -Ala-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 415) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- β -Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 416) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(β -Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 417) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(β -Ala)₂-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 418) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(β -Ala)₂-(Arg)₅-Gln-
- 30 (Arg)₃-NH₂;

- (SEQ ID NO: 419) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-Tyr-Gly-(Arg)₅ - Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 420) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 421) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 422) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)₂-Tyr-Gly-(Arg)₅ - Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 423) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)₂-Gly-(Arg)₅-Gln-
- 10 (Arg)₃-NH₂;
- (SEQ ID NO: 424) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 425) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 426) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-(Arg)₅ -Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 427) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-Gly-(Arg)₅ - Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 428) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-(Arg)₅-Gln-
- 20 (Arg)₄-NH₂;
- (SEQ ID NO: 429) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)₂ -Tyr-Gly-(Arg)₅ -Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 430) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)₂-(Arg)₅ - Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 431) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)₂ -Gly-(Arg)₅ -Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 432) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 433) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-Tyr-Gly-
- 30 (Arg)₅-Gln-(Arg)₃-NH₂;

- (SEQ ID NO: 434) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 435) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 436) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 437) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 438) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)₂-(Arg)₅-Gln-
- 10 (Arg)₃-NH₂;
- (SEQ ID NO: 439) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)₂-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 440) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- 15 (SEQ ID NO: 441) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 442) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 443) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)₂-Tyr-
- 20 Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 444) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 445) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 446) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 447) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 448) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-Tyr-
- 30 Gly-(Arg)₅-Gln-(Arg)₄-NH₂;

- (SEQ ID NO: 449) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 450) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 5 (SEQ ID NO: 451) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 452) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 453) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;
- 10 (SEQ ID NO: 454) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 455) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- 15 (SEQ ID NO: 456) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 457) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 458) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 459) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 460) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 461) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 462) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 463) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- 30

- (SEQ ID NO: 464) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 465) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 466) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 467) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 468) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-
- 10 (Arg)₃-NH₂;
- (SEQ ID NO: 469) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 470) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 471) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-
- 15 NH₂;
- (SEQ ID NO: 472) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 473) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 474) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-
- 20 (Arg)₄-NH₂;
- (SEQ ID NO: 475) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 476) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 25 (SEQ ID NO: 477) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 478) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 479) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 480) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-
- 30 (Arg)₄-NH₂;
- (SEQ ID NO: 481) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;

- (SEQ ID NO: 482) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 483) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 484) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 5 (SEQ ID NO: 485) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 486) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 10 (SEQ ID NO: 487) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 488) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 489) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 490) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 491) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 492) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 493) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 494) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 25 (SEQ ID NO: 495) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 496) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 30 (SEQ ID NO: 497) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;

- (SEQ ID NO: 498) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 499) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- 5 (SEQ ID NO: 500) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 501) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 502) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 10 (SEQ ID NO: 503) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 504) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- 15 (SEQ ID NO: 505) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 506) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 507) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- 20 (SEQ ID NO: 508) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 509) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- 25 (SEQ ID NO: 510) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 511) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 512) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 30

- (SEQ ID NO: 513) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 514) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 5 (SEQ ID NO: 515) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 516) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 517) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₃-NH₂;
- 10 (SEQ ID NO: 518) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 519) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 520) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)₅-Gln-
- 15 (Arg)₄-NH₂;
- (SEQ ID NO: 521) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 522) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- (SEQ ID NO: 523) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)₂-(Arg)₅-Gln-(Arg)₄-
- 20 NH₂;
- (SEQ ID NO: 524) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 525) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 526) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-
- 25 (Arg)₃-NH₂;
- (SEQ ID NO: 527) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₃-NH₂;
- (SEQ ID NO: 528) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂;
- 30 (SEQ ID NO: 529) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-(Arg)₅-Gln-(Arg)₄-NH₂;

(SEQ ID NO: 530) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)₂-Tyr-Gly-(Arg)₅-Gln-(Arg)₄-NH₂; and

(SEQ ID NO: 531) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)₂-(Arg)₅-Gln-(Arg)₄-NH₂,

5 or pharmaceutically acceptable salts thereof.

In some embodiments, a compound of Formula (V) is disclosed in International Application Publication Number WO 2007/008684, which is incorporated herein by reference in its entirety.

10 In some embodiments, the MC4R agonist is a compound of Formula (VI):

Ac-c(Cys-Glu-His-A¹-Arg-A²-A³-Cys)-(Pro)₂-Lys-Asp-NH₂ (VI)

or pharmaceutically acceptable salts thereof. In Formula (VI):

A¹ is the D-isomer of X-Phe or 2-Nal where X is halogen;

A² is Bal, 1-Nal, 2-Nal, or Trp; and

15 A³ is Aib, Ala, β-Ala or Gly,

In some embodiments, the compound of Formula (VI) is selected from:

(SEQ ID NO: 532) Ac-c(Cys-Glu-His-D-4-Br-Phe-Arg-Trp-Gly-Cys)-(Pro)₂-Lys-Asp-NH₂;

(SEQ ID NO: 533) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)₂-Lys-Asp-NH₂;

(SEQ ID NO: 534) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-NH₂;

20 (SEQ ID NO: 535) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)₂-Lys-Asp-NH₂;

(SEQ ID NO: 536) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)₂-Lys-Asp-NH₂;

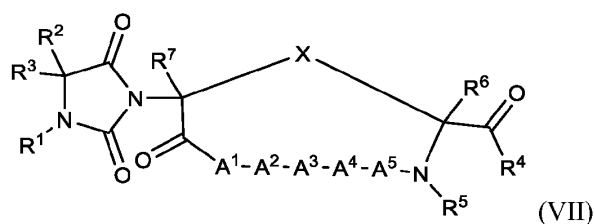
(SEQ ID NO: 537) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-β-Ala-Cys)-(Pro)₂-Lys-Asp-NH₂;

and

(SEQ ID NO: 538) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Aib-Cys)-(Pro)₂-Lys-Asp-NH₂,

25 or pharmaceutically acceptable salts thereof.

In an example embodiment, the MC4R agonist is a compound of Formula (VII):



or a pharmaceutically acceptable salt thereof wherein:

X is selected from the group consisting of -CH₂-S-S-CH₂-, -C(CH₃)₂-S-S-CH₂-, -CH₂-S-S-C(CH₃)₂-, -C(CH₃)₂-S-S-C(CH₃)₂-, -(CH₂)₂-S-S-CH₂-, -CH₂-S-S-(CH₂)₂-, -(CH₂)₂-S-S-(CH₂)₂-, -C(CH₃)₂-S-S-(CH₂)₂-, -(CH₂)₂-S-S-C(CH₃)₂-, -(CH₂)_r-C(O)-NR⁸-(CH₂)_r- and - (CH₂)_r-NR⁸-C(O)-(CH₂)_r;

each of R¹ and R⁵ is, independently, H, (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)alkyl;

each of R² and R³ is, independently, H, (C₁-C₁₀)alkyl, (C₁-C₁₀)heteroalkyl, aryl(C₁-C₅)alkyl, substituted (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)heteroalkyl or substituted aryl(C₁-C₅)alkyl or R² and R³ may be fused together to form a ring;

R⁴ is OH or NH₂;

each of R⁶ and R⁷ is, independently, H, (C₁-C₁₀)alkyl or substituted (C₁-C₁₀)alkyl;

A¹ is an L- or D-amino acid or deleted;

A² is H is, 2-Pal, 3-Pal, 4-Pal, (X¹, X², X³, X⁴, X⁵)Phe, Taz, 2-Thi or 3-Thi;

A³ is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-(X¹, X², X³, X⁴, X⁵)Phe;

A⁴ is Arg, hArg, Dab, Dap, Lys or Orn;

A⁵ is Bal, 1-Nal, 2-Nal, (X¹, X², X³, X⁴, X⁵)Phe or Trp;

r is, independently for each occurrence thereof, 1, 2, 3, 4 or 5; and

t is, independently for each occurrence thereof, 1 or 2;

or pharmaceutically acceptable salts thereof.

In an example embodiment of the compounds of Formula (VII),

A¹ is Ala, D-Ala, Asn, Asp, Gln, Glu or Gly.

Example compounds according to Formula (VII) include:

(SEQ ID NO: 539) c[Hydantoin(C(O)-(Nle-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;

(SEQ ID NO: 540) c[Hydantoin(C(O)-(Ala-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;

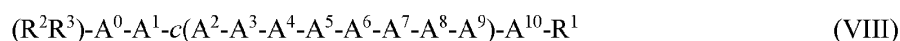
(SEQ ID NO: 541) c[Hydantoin(C(O)-(D-Ala-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;

(SEQ ID NO: 542) c[Hydantoin(C(O)-(Aib-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;

- (SEQ ID NO: 543) c[Hydantoin(C(O)-(Val-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 544) c[Hydantoin(C(O)-(Abu-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 545) c[Hydantoin(C(O)-(Leu-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 546) c[Hydantoin(C(O)-(Ile-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;
 5 (SEQ ID NO: 547) c[Hydantoin(C(O)-(Cha-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 548) c[Hydantoin(C(O)-(A6c-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 549) c[Hydantoin(C(O)-(Phe-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂;
 (SEQ ID NO: 550) c[Hydantoin(C(O)-(Gly-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH₂; and
 (SEQ ID NO: 551) c[Hydantoin(C(O)-(Gly-Cys))-Glu-His-D-Phe-Arg-Trp-Cys]-NH₂,
 10 or pharmaceutically acceptable salts thereof.

In some embodiments, a compound of Formula (VII) is disclosed in International Application Publication Number WO2008/147556, which is incorporated herein by reference in its entirety.

- 15 In some embodiments, the MC4R agonist is a compound of Formula (VIII):



or a pharmaceutically acceptable salt thereof wherein:

- A⁰ is an aromatic amino acid
 A¹ is Acc, HN-(CH₂)_m-C(O), an L- or D-amino acid;
 20 A² is Asp, Cys, D-Cys, hCys, D-hCys, Glu, Pen, or D-Pen;
 A³ is Aib, Ala, β-Ala, Gaba, Gly or a D-amino acid;
 A⁴ is H is, 2-Pal, 3-Pal, 4-Pal, (X¹, X², X³, X⁴, X⁵)Phe, Taz, 2-Thi, or 3-Thi;
 A⁵ is D-Bal, D-1-Nal, D-2-Nal, D-Phe, L-Phe, D-(X¹, X², X³, X⁴, X⁵)Phe, L-Phe, D-Trp or D-(Et)Tyr;
 25 A⁶ is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH((CH₂)_n-N(R⁴R⁵))-C(O);
 A⁷ is Bal, D-Bal, Bip, D-Bip, 1-Nal, D-1-Nal, 2-Nal, D-2-Nal, or D-Trp;
 A⁸ is Acc, Aha, Ahx, Ala, D-Ala, β-Ala, Apn, Gaba, Gly, HN-(CH₂)_s-C(O), or
 deleted;
 A⁹ is Cys, D-Cys, hCys, D-hCys, Dab, Dap, Lys, Orn, Pen, or D-Pen;
 30 A¹⁰ is Acc, HN-(CH₂)_r-C(O), L- or D-amino acid, or deleted;
 R¹ is OH, or NH₂;

- each of R² and R³ is, independently for each occurrence selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₁-C₃₀)heteroalkyl, (C₁-C₃₀)acyl, (C₂-C₃₀)alkenyl, (C₂-C₃₀)alkynyl, aryl(C₁-C₃₀)alkyl, aryl(C₁-C₃₀)acyl, substituted (C₁-C₃₀)alkyl, substituted (C₁-C₃₀)heteroalkyl, substituted (C₁-C₃₀)acyl, substituted (C₂-C₃₀)alkenyl, substituted (C₂-C₃₀)alkynyl, substituted aryl(C₁-C₃₀)alkyl, and substituted aryl(C₁-C₃₀)acyl;
- each of R⁴ and R⁵ is, independently for each occurrence, H, (C₁-C₄₀)alkyl, (C₁-C₄₀)heteroalkyl, (C₁-C₄₀)acyl, (C₂-C₄₀)alkenyl, (C₂-C₄₀)alkynyl, aryl(C₁-C₄₀)alkyl, aryl(C₁-C₄₀)acyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl, substituted (C₁-C₄₀)acyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl, substituted aryl(C₁-C₄₀)alkyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl, or -C(NH)-NH₂;
- m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;
- n is, independently for each occurrence, 1, 2, 3, 4 or 5;
- s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;
- t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;
- X¹, X², X³, X⁴, and X⁵ each is, independently for each occurrence, H, F, Cl, Br, I, (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, substituted (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, substituted (C₂-C₁₀)alkynyl, aryl, substituted aryl, OH, NH₂, NO₂, or CN.
- In example embodiments of Formula (VIII)
- (I) when R⁴ is (C₁-C₄₀)acyl, aryl(C₁-C₄₀)acyl, substituted (C₁-C₄₀)acyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl, or -C(NH)-NH₂, then R⁵ is H or (C₁-C₄₀)alkyl, (C₁-C₄₀)heteroalkyl, (C₂-C₄₀)alkenyl, (C₂-C₄₀)alkynyl, aryl(C₁-C₄₀)alkyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl, or substituted aryl(C₁-C₄₀)alkyl;
- (II) when R² is (C₁-C₃₀)acyl, aryl(C₁-C₃₀)acyl, substituted (C₁-C₃₀)acyl, or substituted aryl(C₁-C₃₀)acyl, then R³ is H, (C₁-C₃₀)alkyl, (C₁-C₃₀)heteroalkyl, (C₂-C₃₀)alkenyl, (C₂-C₃₀)alkynyl, aryl(C₁-C₃₀)alkyl, substituted (C₁-C₃₀)alkyl, substituted (C₁-C₃₀)heteroalkyl, substituted (C₂-C₃₀)alkenyl, substituted (C₂-C₃₀)alkynyl, or substituted aryl(C₁-C₃₀)alkyl;
- (III) when A² is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen, then A⁹ is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen;
- (IV) when A² is Asp or Glu, then A⁹ is Dab, Dap, Orn, or Lys;

(V) when A⁸ is Ala or Gly, then A¹ is not Nle; or pharmaceutically acceptable salts thereof.

In example embodiments of compounds of Formula (VIII):

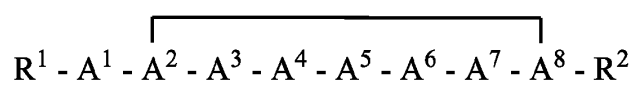
A⁰ is 1-Nal, 2-Nal, H is, Pff, Phe, Trp, or Tyr; A¹ is Arg; A² is Cys; A³ is D-Ala; A⁴ is H; A⁵ is D-Phe; A⁶ is Arg; A⁷ is Trp; A⁸ is deleted; A⁹ is Cys; and A¹⁰ is deleted; or pharmaceutically acceptable salts thereof.

Particular compounds of the immediately foregoing group of Formula (VIII) compounds include:

(SEQ ID NO: 552) Ac-Tyr-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 10 (SEQ ID NO: 553) Ac-2-Nal-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 554) Ac-1-Nal-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 555) Ac-Phe-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 556) Ac-Trp-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 557) Ac-Pff-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 15 (SEQ ID NO: 558) H-His-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂; and
 (SEQ ID NO: 559) Ac-His-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂,
 or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is an agonist described in WO2014/144260 A1, incorporated herein by reference.

In one example embodiment, an MC4R agonist is a compound represented by formula (IX):



or a pharmaceutically acceptable salt thereof, wherein:

25 R¹ is H, or a (C₁-C₆)acyl;

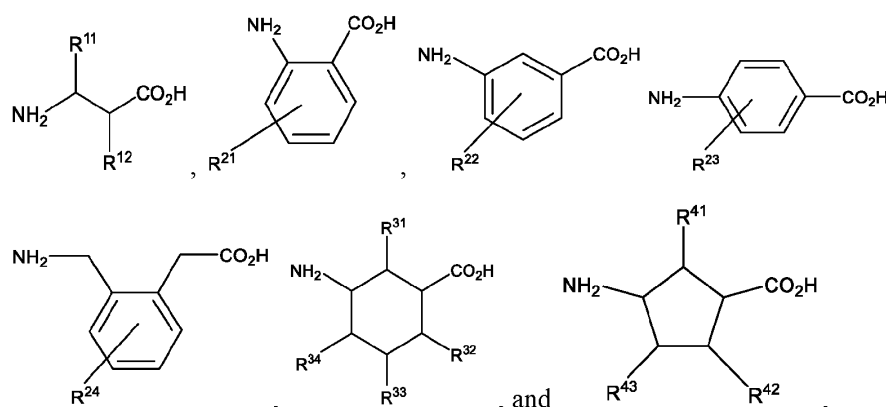
R² is, -NR³R⁴, or -OR⁵ wherein R³, R⁴, and R⁵ are each independently is H or a (C₁-C₆)alkyl;

A¹ is an amino acid residue selected from Arg, Lys, Orn, His, Nle, Phe, Val, Leu, Trp, Tyr, Ala, Ser, Thr, Gln, Asn, Asp, Glu, or TzAla; or

A¹ is a moiety selected from an optionally substituted -(C₁-C₁₂)-alkyl, an optionally substituted -(C₆-C₁₈)-aryl, an optionally substituted -(C₅-C₁₈)-heteroaryl, an aralkyl wherein the aryl portion is an optionally substituted (C₆-C₁₈)aryl, and the alkyl portion is an optionally substituted (C₁-C₁₂)alkyl, or a heteroaralkyl, wherein the heteroaryl portion is an optionally substituted (C₅-C₁₈)heteroaryl, and the alkyl portion is an optionally substituted (C₁-C₁₂)alkyl;

A² and A⁸ is each independently an amino acid residue selected from Cys, hCys, Pen, Asp, Glu, Lys, Orn, Dbu, or Dpr, wherein A² and A⁸ are pairwise selected so as to be able to form covalent bond between their respective side chains;

A³ is absent or is an amino acid residue selected from Ala, Tle, Val, Leu, Ile, Cha, Pro, Ser, Thr, Lys, Arg, His, Phe, Gln, Sar, Gly, Asn, Aib, or residue Y, wherein Y is an amino acid selected from amino acids represented by the following structural formulas



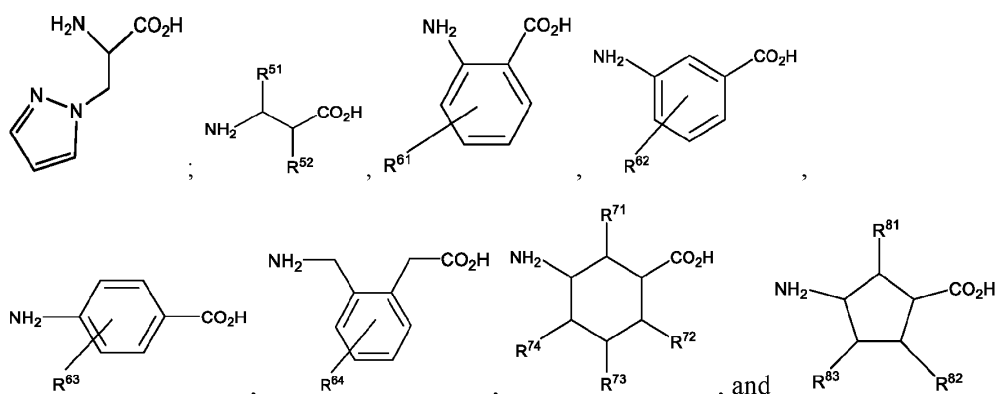
wherein:

R¹¹ and R¹², each independently, is H, -CH₃, phenyl, or benzyl;

R²¹, R²², R²³, and R²⁴, each independently is H, -CH₃, -CF₃, phenyl, benzyl, F, Cl, Br, I, -OCH₃, or -OH;

R³¹, R³², R³³, R³⁴, R⁴¹, R⁴², and R⁴³, each independently is H, -CH₃, -CF₃, phenyl, benzyl, F, Cl, Br, I, -OCH₃, or -OH;

A⁴ is absent or is an amino acid residue selected from Atc, Ala, QAla, Aib, Sar, Ser, Thr, Pro, Hyp, Asn, Gln, an optionally substituted His, Trp, Tyr, Lys, Arg, sChp, or residue X, where the X is an amino acid selected from amino acids represented by the following formulas:



wherein:

R^{51} and R^{52} , each independently, is H, -CH₃, phenyl, or benzyl;

5 R^{61} , R^{62} , R^{63} , and R^{64} , each independently is H, -CH₃, -CF₃, phenyl, benzyl, F, Cl, Br, I, -OCH₃, or -OH;

R^{71} , R^{72} , R^{73} , R^{74} , R^{81} , R^{82} , and R^{83} , each independently is H, -CH₃, -CF₃, phenyl, benzyl, F, Cl, Br, I, -OCH₃, or -OH;

10 A^5 is an optionally substituted Phe, an optionally substituted 1-Nal, or an optionally substituted 2-Nal;

A^6 is Arg; and

A^7 is Trp,

wherein any amino acid residue is either in L- or in D-configuration.

Exemplary compound of Formula (IX) include:

- 15 (SEQ ID NO: 560) Ac-Arg-c(Cys-D-Ala-His-D-Phe(p-F)-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 561) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 562) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe(p-F)-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 563) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe(p-F)-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 564) Ac-Arg-c(Cys-D-Ala-Ser-D-Phe(p-F)-Arg-Trp-Cys)-NH₂;
 20 (SEQ ID NO: 565) Ac-Arg-c(Cys-D-Ala-Thr-D-Phe(p-CN)-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 566) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 567) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 568) Ac-Arg-c(Cys-D-Ala-Trp-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 569) Ac-Arg-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂;
 25 (SEQ ID NO: 570) Ac-Arg-c(Cys-D-Val-Gln-D-Phe-Arg-Trp-Cys)-NH₂;

(SEQ ID NO: 571) Ac-Arg-c(Cys-D-Val-Pro-D-Phe-Arg-Trp-Cys)-NH₂; and
 (SEQ ID NO: 572) Ac-Arg-c(Cys-D-Ser-Pro-D-Phe-Arg-Trp-Cys)-NH₂,
 or a pharmaceutically acceptable salt thereof.

- 5 In yet another embodiment, the polypeptides of the present invention include any one of the following structural formulas:
- (SEQ ID NO: 573) Ac-Arg-c(hCys-D-Ala-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 574) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 575) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Cys)-OH;
 10 (SEQ ID NO: 576) Ac-Arg-c(Cys-D-Ala-D-Phe-Arg-Trp-hCys)-NH₂;
 (SEQ ID NO: 577) Ac-Arg-c(Pen-D-Ala-D-Phe-Arg-Trp-hCys)-NH₂;
 (SEQ ID NO: 578) Ac-Arg-c(hCys-D-Ala-D-Phe(p-F)-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 579) Ac-Arg-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 580) Ac-Nle-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH₂;
 15 (SEQ ID NO: 581) Arg-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 582) CH₃-(CH₂)₄-CO-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH₂; and
 (SEQ ID NO: 583) Benzyl-CO-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH₂,
 or a pharmaceutically acceptable salt thereof.

- 20 In a further embodiment, the polypeptides of the present invention include the polypeptide represented by any one of the following structural formulas:
- (SEQ ID NO: 584) Ac-Arg-c(Asp-D-Ala-D-Phe-Arg-Trp-Dbu)-NH₂;
 (SEQ ID NO: 585) Ac-Arg-c(Glu-D-Ala-D-Phe-Arg-Trp-Dpr)-NH₂;
 (SEQ ID NO: 586) Ac-Arg-c(Glu-Ala-D-Phe-Arg-Trp-Dpr)-NH₂;
 (SEQ ID NO: 587) Ac-Arg-c(Dpr-D-Ala-D-Phe-Arg-Trp-Glu)-NH₂;
 25 (SEQ ID NO: 588) Ac-Arg-c(Dpr-D-Ala-D-Phe(4-F)-Arg-Trp-Glu)-NH₂;
 (SEQ ID NO: 589) Ac-Arg-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH₂;
 (SEQ ID NO: 590) Ac-Arg-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-OH;
 (SEQ ID NO: 591) Ac-Nle-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH₂;
 (SEQ ID NO: 592) Arg-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH₂;
 30 (SEQ ID NO: 593) CH₃-(CH₂)₄-CO-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH₂; or
 (SEQ ID NO: 594) Benzyl-CO-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH₂,

or a pharmaceutically acceptable salt thereof.

- In yet another embodiment, the polypeptides of the present invention include a polypeptide represented by Formula (IV), wherein A⁴ is an amino acid residue selected from
- 5 Atc, Ala, QAla, Aib, Sar, Ser, Thr, Pro, Hyp, Asn, Gln, a substituted His, Trp, Tyr, Lys, Arg, sChp, or residue X. Examples of such peptides include peptides represented by any one of the following structural formulas:
- (SEQ ID NO: 595) Ac-Arg-c(Cys-D-Ala-His(3-Me)-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 596) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-Phe-Arg-Trp-Cys)-NH₂;
10 (SEQ ID NO: 568) Ac-Arg-c(Cys-D-Ala-Trp-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 567) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 566) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 597) Ac-Arg-c(Cys-D-Ala-Arg-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 598) Ac-Arg-c(Cys-D-Ala-Tyr-D-Phe-Arg-Trp-Cys)-NH₂;
15 (SEQ ID NO: 599) Ac-Arg- c(Cys-D-Ala-D-Pro-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 561) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 563) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe(p-F)-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 600) Ac-Arg- c(Cys-D-Ala-Atc-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 601) Ac-Arg- c(Cys-D-Ala-QAla-D-Phe-Arg-Trp-Cys)-NH₂;
20 (SEQ ID NO: 602) Ac-Arg- c(Cys-D-Ala-sChp-D-Phe-Arg-Trp-Cys)-NH₂; or
(SEQ ID NO: 603) Ac-Arg- c(Cys-D-Ala-X-D-Phe-Arg-Trp-Cys)-NH₂,
or a pharmaceutically acceptable salt thereof.

- In example embodiments, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:
- 25 (SEQ ID NO: 574) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 573) Ac-Arg-c(hCys-D-Ala-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 604) Ac-Arg-c(hCys-D-Ala-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 585) Ac-Arg-c(Glu-D-Ala-D-Phe-Arg-Trp-Dpr)-NH₂;
(SEQ ID NO: 586) Ac-Arg-c(Glu-Ala-D-Phe-Arg-Trp-Dpr)-NH₂;
30 (SEQ ID NO: 605) Ac-Arg-c(hCys-Aib-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 606) Ac-Arg-c(hCys-Sar-D-Phe-Arg-Trp-Cys)-NH₂;

- (SEQ ID NO: 607) Ac-Arg-c(hCys-Val-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 608) Ac-Arg-c(hCys-D-Val-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 609) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 610) Ac-Arg-c(hCys-D-Gln-D-Phe-Arg-Trp-Cys)-NH₂;
 5 (SEQ ID NO: 611) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 612) Ac-Arg-c(D-Pen-D-Ala-D-Phe-Arg-Trp-hCys)-NH₂;
 (SEQ ID NO: 576) Ac-Arg-c(Cys-D-Ala-D-Phe-Arg-Trp-hCys)-NH₂;
 (SEQ ID NO: 613) Ac-Arg-c(Pen-D-Ala-D-Phe-Arg-Trp-hCys)-NH₂;
 (SEQ ID NO: 614) Ac-Arg-c(D-hCys-D-Ala-D-Phe-Arg-Trp-Cys)-NH₂;
 10 (SEQ ID NO: 579) Ac-Arg-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH₂; or
 (SEQ ID NO: 615) Ac-Arg-c(hCys-D-Pro-D-Phe-Arg-Trp-Cys)-NH₂,
 or a pharmaceutically acceptable salt thereof.

- In another embodiment, the polypeptides of the present invention include polypeptides represented by Formula (IV), wherein A³ is an amino acid residue selected from
 15 Tle, Val, Leu, Ile, Cha, Pro, Ser, Thr, Lys, Arg, His, Phe, Gln, Sar, Gly, Asn, or Aib; and A⁴ is an amino acid residue selected from Atc, Ala, QAla, Aib, Sar, Ser, Thr, Pro, Hyp, Asn, Gln, a substituted His, Trp, Tyr, Lys, Arg, sChp, or residue X. Examples of such polypeptides are polypeptides represented by any one of the following structural formulas:
 (SEQ ID NO: 616) Ac-Arg-c(Cys-Val-Gln-D-Phe-Arg-Trp-Cys)-NH₂;
 20 (SEQ ID NO: 570) Ac-Arg-c(Cys-D-Val-Gln-D-Phe-Arg-Trp-Cys)-NH₂; or
 (SEQ ID NO: 617) Ac-Arg-c(Cys-D-Val-His(1-Me)-D-Phe-Arg-Trp-Cys)-NH₂,
 or a pharmaceutically acceptable salt thereof.

- In a further embodiment, the polypeptides of the present invention include a
 25 polypeptide represented by any one of the following structural formulas:
 (SEQ ID NO: 618) Ac-TzAla-c(Cys-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH₂; or
 (SEQ ID NO: 619) Ac-Glu-c(Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂,
 or a pharmaceutically acceptable salt thereof.

- 30 In yet another embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 596) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 567) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH₂; or
(SEQ ID NO: 566) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-NH₂,
or a pharmaceutically acceptable salt thereof.

5

In a further embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 620) Ac-Arg-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 621) Ac-Arg-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH₂;
10 (SEQ ID NO: 622) Ac-Arg-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH₂; or
(SEQ ID NO: 569) Ac-Arg-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂,
or a pharmaceutically acceptable salt thereof.

15 In a further embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

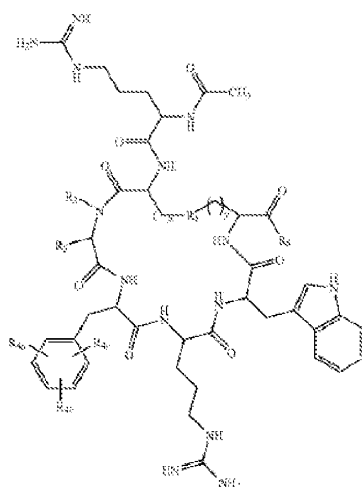
(SEQ ID NO: 623) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 624) Ac-Arg-c(Cys-D-Ala-Gln-D-2-Nal-Arg-Trp-Cys)-NH₂; or
(SEQ ID NO: 625) Ac-Arg-c(Cys-D-Ala-Asn-D-2-Nal-Arg-Trp-Cys)-NH₂,
or a pharmaceutically acceptable salt thereof.

20

In a further embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 626) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-Phe-Arg-Trp-Cys)-OH;
(SEQ ID NO: 627) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-OH; or
25 (SEQ ID NO: 628) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-OH,
or a pharmaceutically acceptable salt thereof.

In one example embodiment, an MC4R agonist is a compound represented by Formula (X):



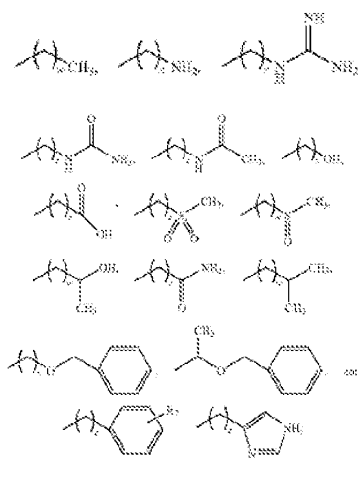
(X)

or a pharmaceutically acceptable salt thereof. In Formula (X), the chemical substituents are defined as follows:

R_1 is $-\text{NH}-\text{C}(\text{O})-$ or $-\text{C}(\text{O})-\text{NH}-$;

- 5 R_2 is $-\text{H}$, $-\text{CH}_2-$, or, R_2 , together with R_3 , forms a pyrrolidine ring optionally substituted with $-\text{OH}$;

R_3 is $-(\text{CH}_2)_2-$ if R_2 is $-\text{CH}_2-$, and otherwise R_3 is selected from



- 10 R^{4a} , R^{4b} , and R^{4c} are each independently selected from hydrogen, halo, $(\text{C}_1-\text{C}_{10})$ alkyl-halo, $(\text{C}_1-\text{C}_{10})$ alkyl-dihalo, $(\text{C}_1-\text{C}_{10})$ alkyl-trihalo, $(\text{C}_1-\text{C}_{10})$ alkyl, $(\text{C}_1-\text{C}_{10})$ alkoxy, $(\text{C}_1-$

C₁₀)alkylthio, aryl, aryloxy, nitro, nitrile, sulfonamide, amino, hydroxyl, carboxy, and alkoxy-carbonyl. In one example embodiment, R^{4a}, R^{4b}, and R^{4c} is not hydrogen.

R⁵ is -OH or -N(R^{6a})(R^{6b});

R^{6a} and R^{6b} are each independently H or C₁ to C₄ linear, branched or cyclic alkyl chain;

R⁷ is -H or -C(O)-NH₂;

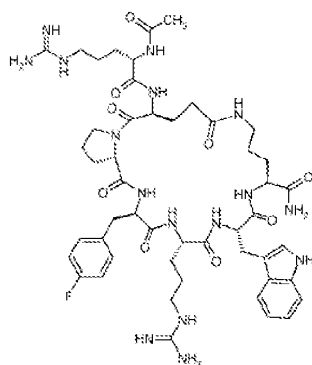
w is in each instance independently 0 to 5;

x is 1 to 5;

y is 1 to 5;

z is in each instance independently 1 to 5.

An example of a compound of Formula (X) is a cyclic peptide defined by Formula (XI):



(XI), or a pharmaceutically acceptable salt thereof.

In one example embodiment, the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof. In another example embodiment, the MC4R agonist is Hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 148) or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is an agonist described in WO2014/144260 A1, incorporated herein by reference.

In one example embodiment, the MC4 agonist is a compound represented by Formula (XII):



Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or
 Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;
 Xxx is Asn, Gln, Ser, Thr;

5 Yyy is Lys, Arg, D-Lys, D-Arg;

A1 is H, Ac;

A₂ is OH, NH₂;

10 In embodiments, the MC4R agonist is chosen from one or more of the following
 compounds, (or pharmaceutically acceptable salt thereof):

(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

15 (SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH₂;

(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

20 (SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

25 (SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

30 (SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

- (SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
5 (SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
10 (SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
15 (SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
20 (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
25 (SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
30 (SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;

- (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 5 (SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 10 (SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂, or
 (SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

15 In some embodiments, the MC4R agonist is a compound of Formula (XII-a):



or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or
 Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

20 Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

In some embodiments, the compound of Formula (XII-a) is selected from:

- (SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 25 (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 30 (SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

- (SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 5 (SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and
 (SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

In some embodiments, the MC4R agonist is a compound of Formula (XII-b):



- 10 or a pharmaceutically acceptable salt thereof, wherein:
 Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or
 Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;
 Xxx is Asn, Gln, Ser, Thr; and
 Yyy is Lys, Arg, D-Lys, D-Arg.
- 15 In some embodiments, the compound of Formula (XII-b) is selected from:
 (SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 20 (SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH₂;
 (SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 25 (SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 30 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and

(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

In some embodiments, the MC4R agonist is a compound of Formula (XII-c):



5 or a pharmaceutically acceptable salt thereof, wherein:

A₁ is H or Ac;

A₂ is OH or NH₂;

Yyy is L-Arg or D-Arg;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide

10 bridge; or

Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and

Xxx is Asn, Gln, Ser, or Thr.

In some embodiments, the compound of Formula (XII-c) is selected from:

(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

15 (SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH₂;

(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

20 (SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

25 (SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

30 (SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

- (SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 5 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 10 (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH; and
 15 (SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH.

In some embodiments, the MC4R agonist is a compound of Formula (XII-d):



or a pharmaceutically acceptable salt thereof, wherein:

A₁ is H or Ac;

- 20 A₂ is OH or NH₂;

Yyy is L-Lys or D-Lys;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and

- 25 Xxx is Asn, Gln, Ser, or Thr.

In some embodiments, the compound of Formula (XII-d) is selected from:

- (SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 30 (SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

- (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
5 (SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
10 (SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
15 (SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
20 (SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
25 (SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂, and
(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

In some embodiments, the MC4R agonist is an agonist described in
30 WO2014/144260 or WO2017/059075, each of which is incorporated herein by
reference. Administration of a compound or pharmaceutically acceptable salt thereof

or a composition comprising a compound or pharmaceutical salt of a compound of the disclosure useful to practice the methods described herein, can be continuous, hourly, four times daily, three time daily, twice daily, once daily, once every other day, twice weekly, once weekly, once every two weeks, once a month, or once every two months, or longer or
5 some other intermittent dosing regimen.

Examples of administration of a compound or composition comprising a compound or pharmaceutical salt of a compound of the disclosure include peripheral administration. Examples of peripheral administration include oral, subcutaneous, intraperitoneal, intramuscular, intravenous, rectal, transdermal or intranasal forms of administration.

10 As used herein, peripheral administration can include all forms of administration of a compound or a composition comprising a compound of the instant disclosure which excludes intracranial administration. Examples of peripheral administration include, but are not limited to, oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, extended release, slow release implant, depot and the like), nasal, vaginal, rectal,
15 sublingual or topical routes of administration, including transdermal patch applications and the like.

The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. Where the amino acid has D and L isomeric forms, it is the L
20 form of the amino acid that is represented unless otherwise explicitly indicated.

The compounds of the disclosure useful for practicing the methods described herein may possess one or more chiral centers and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present disclosure. Racemic compounds may either be separated using preparative HPLC and a column with a
25 chiral stationary phase or resolved to yield individual enantiomers utilizing methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of the disclosure.

The compounds described herein may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present disclosure. For
30 example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form, α -pyridonyl.

The present disclosure further features providing an MC4R agonist in combination with an additional agent. Exemplary agents include a second MC4R agonist (e.g., an agent described herein or elsewhere), or an agent aimed to treat a symptom of obesity or a co-morbidity. For example, the additional agent may be an anti-hypertensive drug, a pain medication, an anti-inflammatory, a lipid-lowering agent, a cardiovascular drug, or a diuretic. The combination therapy may be administered as a single formulation or as separate formulations. In an embodiment, the MC4R agonist and the additional agent are administered as a single pharmaceutical composition. In an embodiment, the MC4R agonist and the additional agent are administered as separate pharmaceutical compositions. In the case of separate formulations, the MC4R agonist and the additional agent may be administered concomitantly or sequentially. In an embodiment, the MC4R agonist and the additional agent are administered concomitantly. In an embodiment, the MC4R agonist and the additional agent are administered sequentially. For example, the MC4R agonist may be administered prior to the additional agent or subsequent to the additional agent.

In some embodiments, the administration of the MC4R agonist and the additional agent has a synergistic or additive effect. For example, the administration of the MC4R agonist and the additional agent may have an additive effect, in which the therapeutic effect of the MC4R agonist and the additional agent is the total sum of the effects of each of the components individually. In contrast, the administration of the MC4R agonist and the additional agent may have a synergistic effect, in which the therapeutic effect of the MC4R agonist and the additional agent is greater than the sum of the individual components. The synergistic effect of the combination of the MC4R agonist and the additional agent may be 0.1%, 0.25%, 0.5%, 0.75%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than the total sum of the effects of the MC4R agonist and the additional agent administered individually. In an embodiment, the synergistic effect of the combination of the MC4R agonist and the additional agent is greater than between 5% and 75% of the total sum of the effects of the MC4R agonist and the additional agent administered individually.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to

which this disclosure belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

Pharmaceutical Compositions/Administration

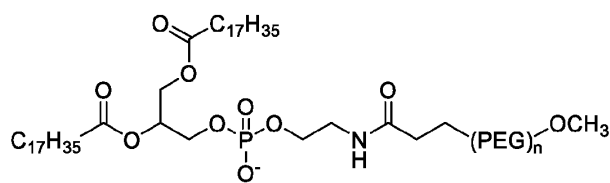
5 In accordance with any method or composition described herein, in embodiments, provided herein is a unit dosage of a MC4R agonist described herein, e.g., setmelanotide. In embodiments, the unit dosage contains 0.1-10 mg, e.g., 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 mg of the MC4R agonist. In embodiments, the unit dosage contains about 0.1,
10 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist. In embodiments, the unit dosage is suitable for injection, e.g., subcutaneous injection. In embodiments, the unit dosage is disposed in a delivery device suitable for injection, e.g., subcutaneous injection. In embodiments, the unit dosage is disposed in a syringe suitable for injection, e.g., subcutaneous injection, or a pen-type injector. Exemplary
15 pen-type injectors are described, e.g., in US 8512297B2, US5688251A, US5820602A, US2014/0163526A1, and US5226895A, incorporated herein by reference.

 In embodiments, also provided herein is a pharmaceutical composition comprising a MC4R agonist described herein, e.g., setmelanotide. In embodiments, the pharmaceutical composition includes a therapeutically effective amount of a MC4R agonist described herein,
20 e.g., setmelanotide. A therapeutically effective amount of the agonist can vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the agonist to elicit a desired response in the individual, e.g., amelioration of at least one disorder parameter, e.g., a parameter of obesity or hyperphagia, or amelioration of at least one symptom of the disorder, e.g., obesity, hyperphagia, a disease or disorder associated with a
25 gene in Table 2, or other obesity-associated genetic disorder. In embodiments, a therapeutically effective amount is also one in which any toxic or a detrimental effect of the composition is outweighed by the therapeutically beneficial effects.

 In certain embodiments, the agonist may be prepared with a carrier that will protect it against rapid release, such as a controlled release formulation, including implants, and
30 microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters,

and polylactic acid. Many methods for the preparation of such formulations are patented or generally known. See, *e.g.*, Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

In other embodiments, the MC4R agonist can be prepared as described in WO2014/144842, incorporated herein by reference. In embodiments, the MC4R agonist is prepared in a formulation comprising an anionic excipient, e.g., PEG-carboxylic acid, fatty acid having 10 or more carbon atoms, and/or anionic phospholipid. In embodiments, the anionic phospholipid is described in WO2014/144842 (e.g., at pages 7-9). In some embodiments, the anionic phospholipid is 1,2-distearoyl-sn-Glycero-3-Phosphoethanolamine (DSPE), optionally conjugated to polyethylene glycol (PEG), the structure of which is:



with the value of “n” varying with molecular weight. In embodiments, the fatty acid is described in WO2014/144842 (e.g., at page 9). In embodiments, the PEG-carboxylic acid is described in WO2014/144842 (e.g., at pages 9-11). In embodiments, the molar ratio of the agonist to the anionic excipient ranges from about 1:1 to about 1:10.

In embodiments, the MC4R agonist forms an ionic complex with the other components of the formulation, and e.g., provides a desirable pharmacokinetic profile for the agonist (e.g., extend duration of drug action and/or minimize adverse effects).

20 In embodiments, the formulation is a sustained release formulation. In embodiments, the formulation provides reduced fluctuations in concentration of the agonist after administration.

In other embodiments, the MC4R agonist can be prepared as described in WO 2019/099735, incorporated herein by reference. In embodiments, the MC4R agonist is prepared in a formulation comprising a neutral diacyl lipid and/or a tocopherol; a phospholipid; an alcohol; and optionally, a polar solvent, *e.g.*, a buffer, optionally comprising an antioxidant. In an embodiment, the neutral diacyl lipid comprises glycerol dioleate (GDO). In an embodiment, the amount of the neutral diacyl lipid

(e.g., GDO) is between 20-80%, 30-70%, 33-60%, or 38-43% by weight, e.g., of the total formulation. In an embodiment, the phospholipid comprises phosphatidylcholine (e.g., soybean phosphatidylcholine). In an embodiment, the amount of the phospholipid (e.g., phosphatidylcholine (e.g., soybean phosphatidylcholine)) is between 20-80%, 30-70%, 33-
5 60%, or 38-43% by weight, e.g., of the total formulation. In an embodiment, the alcohol comprises ethanol. In an embodiment, the amount by weight % of ethanol is greater than 1% by weight, e.g., between 1-20% by weight, e.g., of the total formulation. In an embodiment, the polar solvent, e.g., buffer, comprises citrate buffer, optionally wherein the pH of the buffer is 6.4. In an embodiment, the polar solvent, e.g., buffer, comprises citrate acid
10 monohydrate. In an embodiment, the polar solvent, e.g., buffer, comprises an additional component, e.g., an antioxidant, or a chemical or physical stabilizing agent. In an embodiment, the antioxidant is EDTA.

A MC4R agonist described herein, e.g., setmelanotide, can be administered to a subject, e.g., human subject, by various methods. In some embodiments, pharmaceutical
15 compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous
20 or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and/or to other mucosal surfaces. In embodiments, the route of administration is
25 one of: intravenous injection or infusion, subcutaneous injection, or intramuscular injection. In embodiments, the route of administration is subcutaneous injection.

In embodiments, pharmaceutical compositions, e.g., comprising a MC4R agonist described herein, can be administered with medical devices. For example, compositions comprising the agonist can be administered with a needleless hypodermic injection device,
30 such as the devices disclosed in U.S. Pat. No. 5,399,163, 5,383,851, 5,312,335, 5,064,413, 4,941,880, 4,790,824, or 4,596,556. Examples of implants and modules include: U.S. Pat.

No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Pat. No. 4,486,194, which discloses a therapeutic device for administering medicaments through the skin; U.S. Pat. No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Pat. No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Pat. No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and U.S. Pat. No. 4,475,196, which discloses an osmotic drug delivery system. Other such implants, delivery systems, and modules can also be used.

10 In embodiments, continuous administration can be indicated, e.g., via subcutaneous pump. In embodiments, the agonist is administered via a syringe (e.g., prefilled syringe), an implantable device, a needleless hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

In embodiments, the agonist is administered at a unit dosage, e.g., comprising 15 0.1-10 mg, e.g., 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 mg of the agonist, e.g., subcutaneously.

In embodiments, the MC4R agonist is administered in a bolus at a dose of between 0.1-10 mg, e.g., 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 20 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 mg of the MC4R agonist, e.g., subcutaneously.

In embodiments, the MC4R agonist is administered continuously, e.g., via a pump, e.g., subcutaneous pump.

In embodiments, the MC4R agonist, e.g., a unit dosage of the MC4R agonist, 25 is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe), an implantable device, a needleless hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

In embodiments, a daily dosage of the MC4R agonist is administered, e.g., subcutaneously, to a subject. In embodiments, the daily dosage of the MC4R agonist 30 is about 0.1 mg to about 10 mg, e.g., 0.1-0.2, 0.2-0.4, 0.4-0.6, 0.6-0.8, 0.8-1, 1-1.2,

1.2-1.5, 1.5-2, 2-2.5, 2.5-3, 3-3.5, 3.5-4, 4-4.5, 4.5-5, 5-5.5, 5.5-6, 6-6.5, 6.5-7, 7-7.5, 7.5-8, 8-8.5, 8.5-9, 9-9.5, 9.5-10 mg, e.g., administered subcutaneously.

In embodiments, the MC4R agonist, e.g., setmelanotide, is administered, e.g., via one or multiple administrations, over a period of at least 3 weeks, e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more. In embodiments, where multiple administrations are provided of the MC4R agonist, the time interval in between any two of the administrations is at least 6 hours, e.g., 6 h, 12 h, 24 h, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, or more. In embodiments, the interval in between any two of the administrations is 1 day.

Kits

A MC4R agonist described herein, e.g., setmelanotide, can be provided in a kit. The kit may include a MC4R agonist described herein and, optionally, a container, a pharmaceutically acceptable carrier and/or informational material. The informational material can be descriptive, instructional, marketing or other material that relates to the methods described herein and/or the use of the MC4R agonist for the methods described herein.

The informational material of the kits is not limited in its form. In one embodiment, the informational material can include information about production of the MC4R agonist, physical properties of the MC4R agonist, concentration, date of expiration, batch or production site information, and so forth. In one embodiment, the informational material relates to methods for administering the MC4R agonist, e.g., by a route of administration described herein and/or at a dose and/or dosing schedule described herein.

In one embodiment, the informational material can include instructions to administer an MC4R agonist described herein in a suitable manner to perform the methods described herein, e.g., in a suitable dose, dosage form, or mode of administration (e.g., a dose, dosage form, or mode of administration described herein). In another embodiment, the informational material can include instructions to administer an MC4R agonist to a suitable subject, e.g., a

human, *e.g.*, an obese human, *e.g.*, severely obese human, *e.g.*, having a disease or disorder associated with a gene in Table 2.

The informational material of the kits is not limited in its form. In many cases, the informational material, *e.g.*, instructions, is provided in printed matter, *e.g.*, a printed text, drawing, and/or photograph, *e.g.*, a label or printed sheet. However, the informational material can also be provided in other formats, such as Braille, computer readable material, video recording, or audio recording. In another embodiment, the informational material of the kit is contact information, *e.g.*, a physical address, email address, website, or telephone number, where a user of the kit can obtain substantive information about an MC4R agonist described herein and/or its use in the methods described herein. The informational material can also be provided in any combination of formats.

In addition to an MC4R agonist, the composition of the kit can include other ingredients, such as a surfactant, a lyo-protectant or stabilizer, an antioxidant, an antibacterial agent, a bulking agent, a chelating agent, an inert gas, a tonicity agent and/or a viscosity agent, a solvent or buffer, a stabilizer, a preservative, a pharmaceutically acceptable carrier and/or a second agent for treating a condition or disorder described herein. Alternatively, the other ingredients can be included in the kit, but in different compositions or containers than an MC4R agonist described herein.

In some embodiments, a component of the kit is stored in a sealed vial, *e.g.*, with a rubber or silicone closure (*e.g.*, a polybutadiene or polyisoprene closure). In some embodiments, a component of the kit is stored under inert conditions (*e.g.*, under Nitrogen or another inert gas such as Argon). In some embodiments, a component of the kit is stored under anhydrous conditions (*e.g.*, with a desiccant). In some embodiments, a component of the kit is stored in a light blocking container such as an amber vial.

An MC4R agonist described herein can be provided in any form, *e.g.*, liquid, frozen, dried or lyophilized form. It is preferred that a composition including the MC4R agonist described herein be substantially pure and/or sterile. When an MC4R agonist described herein such as setmelanotide is provided in a liquid solution, the

liquid solution preferably is an aqueous solution, with a sterile aqueous solution being preferred. In one embodiment, the MC4R agonist is supplied with a diluents or instructions for dilution. The diluent can include for example, a salt or saline solution, *e.g.*, a sodium chloride solution having a pH between 6 and 9, lactated Ringer's injection solution, D5W, or PLASMA-LYTE A Injection pH 7.4[®] (Baxter, Deerfield, IL).

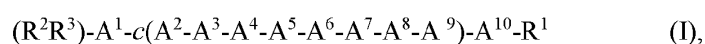
- The kit can include one or more containers for the composition containing an MC4R agonist described herein. In some embodiments, the kit contains separate containers, dividers or compartments for the composition and informational material. For example, the composition can be contained in a bottle, vial, IV admixture bag, IV infusion set, piggyback set or syringe (*e.g.*, prefilled syringe), and the informational material can be contained in a plastic sleeve or packet. In other embodiments, the separate elements of the kit are contained within a single, undivided container. For example, the composition is contained in a bottle, vial or syringe that has attached thereto the informational material in the form of a label. In embodiments, the composition is contained in an injector device, *e.g.*, a pen-type injector.
- The containers of the kits can be airtight or waterproof (*e.g.*, impermeable to changes in moisture or evaporation).

EXEMPLARY ENUMERATED EMBODIMENTS

1. A method of treating a non-genetic obesity in a subject comprising administering to the subject a melanocortin-4 receptor (MC4R) agonist, wherein the subject:
 - (i) has or is identified as having a non-genetic obesity;
 - (ii) has or is identifying as having damage to the brain tissue; and/or
 - (iii) has or is identified as having a proliferative brain disease,
 thereby treating the non-genetic obesity in the subject.
2. The method of embodiment 1, comprising (i).
3. The method of any one of the preceding embodiments, comprising (ii).
4. The method of any one of the preceding embodiments, comprising (iii).

5. The method of any one of the preceding embodiments, wherein the non-genetic obesity comprises obesity is caused by a neurodevelopmental abnormality or a brain malformation.
- 5 6. The method of any one of the preceding embodiments, wherein the damage to the brain tissue is present in the hypothalamus.
7. The method of embodiment 6, wherein the damage to the brain tissue is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or arcuate hypothalamic nucleus.
- 10
8. The method of embodiment 7, wherein the damage or trauma in the brain occurs in the ventromedial nucleus.
- 15 9. The method of any one of the preceding embodiments, wherein the non-genetic obesity comprises hypothalamic obesity.
10. The method of any one of the preceding embodiments, wherein the proliferative brain disease comprises a benign tumor, a benign lesion, or a malignant tumor (e.g., cancer).
- 20
11. The method of embodiment 10, wherein the proliferative brain disease is present in the hypothalamus.
12. The method of any one of embodiments 10 or 11, wherein the proliferative brain disease is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or arcuate hypothalamic nucleus.
- 25
13. The method of any one of embodiments 10-12, wherein the proliferative brain disease comprises craniopharyngioma or astrocytoma.
- 30

14. The method of any one of the preceding embodiments, wherein the subject has undergone a surgery (e.g., tumor removal or bariatric surgery) or received radiation.
15. The method of any one of the preceding embodiments, wherein the subject is obese,
5 e.g., severely obese.
16. The method of any one of the preceding embodiments, wherein the subject is hyperphagic.
- 10 17. The method of any one of the preceding embodiments, wherein the subject has a body mass index (BMI) greater than 35 kg/m² (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.
- 15 18. The method of any one of the preceding embodiments wherein the subject has a body mass index (BMI) greater than 40 kg/m² (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.
- 20 19. The method of any one of the preceding embodiments, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.
- 25 20. The method of any one of the preceding embodiments, wherein the subject has a lower body weight after administration of the MC4R agonist than before administration of the MC4R agonist.
21. The method of any one of the preceding embodiments, wherein the MC4R agonist is
30 has the structure of Formula (I):



wherein:

A¹ is Acc, HN—(CH₂)_m—C(O), L- or D-amino acid, or deleted;

A² is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A³ is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

5 A⁴ is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X¹, X², X³, X⁴, X⁵)Phe;

A⁵ is D-Phe, Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X¹, X², X³, X⁴,
X⁵)Phe, or D-(Et)Tyr;

A⁶ is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH((CH₂)_n-N(R⁴R⁵))-C(O);

A⁷ is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

10 A⁸ is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-(CH₂)_s-C(O),
or deleted;

A⁹ is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A¹⁰ is Acc, HN-(CH₂)_t-C(O), L- or D-amino acid, or deleted;

R¹ is OH or NH₂;

15 each of R² and R³ is, independently for each occurrence, selected from the
group consisting of H, (C₁-C₃₀)alkyl, (C₁-C₃₀)heteroalkyl, (C₁-C₃₀)acyl, (C₂-
C₃₀)alkenyl, (C₂-C₃₀)alkynyl, aryl(C₁-C₃₀)alkyl, aryl(C₁-C₃₀)acyl, substituted (C₁-
C₃₀)alkyl, substituted (C₁-C₃₀)heteroalkyl, substituted (C₁-C₃₀)acyl, substituted (C₂-
C₃₀)alkenyl, substituted (C₂-C₃₀)alkynyl, substituted aryl(C₁-C₃₀)alkyl, and
20 substituted aryl(C₁-C₃₀)acyl;

each of R⁴ and R⁵ is, independently for each occurrence, H, (C₁-C₄₀)alkyl, (C₁-
C₄₀)heteroalkyl, (C₁-C₄₀)acyl, (C₂-C₄₀)alkenyl, (C₂-C₄₀)alkynyl, aryl(C₁-C₄₀)alkyl,
aryl(C₁-C₄₀)acyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl,
substituted (C₁-C₄₀)acyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl,
25 substituted aryl(C₁-C₄₀)alkyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl,
or -C(NH)-NH₂;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

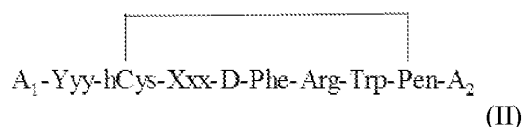
s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

30 t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X¹, X², X³, X⁴, and X⁵ each is, independently for each occurrence, H, F, Cl, Br, I, (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, substituted (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, substituted (C₂-C₁₀)alkynyl, aryl, substituted aryl, OH, NH₂, NO₂, or CN.

- 5 22. The method of embodiment 21, wherein A¹ is selected from Lys, D-Lys, Arg, and D-Arg.
23. The method of embodiment 21, wherein A² and A⁹ are each independently selected from Cys, hCys, and Pen.
- 10 24. The method of embodiment 21, wherein A³ is selected from Ala or D-Ala.
25. The method of embodiment 21, wherein A⁴ is selected from His and D-His.
- 15 26. The method of embodiment 21, wherein A⁵ is selected from Phe, D-Phe, D-1-Nal, and D-2-Nal.
27. The method of embodiment 21, wherein A⁶ is Arg.
- 20 28. The method of embodiment 21, wherein A⁷ is Trp.
29. The method of embodiment 21, wherein A⁸ and/or A¹⁰ is deleted.
30. The method of embodiment 21, wherein R¹ is NH₂.
- 25 31. The method of embodiment 21, wherein one of R² and R³ is independently hydrogen and the other of R² and R³ is independently (C₁-C₃₀) acyl (e.g., acetyl).
32. The method of any one of the preceding embodiments, wherein the MC4R agonist is
- 30 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140).

33. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (II) or a pharmaceutically acceptable salt thereof:



- 5 where Xxx is Asn, Gln, Ser, or Thr,
 where A₁ is H or Ac,
 where A₂ is OH or NH₂, and
 where Yyy is Lys, Arg, D-Lys, or D-Arg.
- 10 34. The method of embodiment 33, wherein the MC4R agonist is selected from:
 SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 15 (SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH₂;
 (SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 20 (SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 25 (SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

- (SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
5 (SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
10 (SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
15 (SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
20 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
25 (SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
30 (SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

- (SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
5 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
10 (SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and
15 (SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂,
or a pharmaceutically acceptable salt thereof.

35. The method of any one of the preceding embodiments, wherein the MC4R agonist is formulated as a pharmaceutical composition.
20
36. The method of embodiment 35, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.
37. The method of embodiment 35, wherein the pharmaceutical composition comprises a
25 polyethylene glycol (e.g., a modified polyethylene glycol, e.g., mPEG-DSPE, e.g., mPEG-2,000-DSPE).
38. The method of any one of the preceding embodiments, comprising administering the
30 MC4R agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

39. The method of embodiment 38, wherein the unit dosage form is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe), an implantable device, a needleless hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.
- 5
40. The method of embodiment 39, wherein the MC4R agonist is administered subcutaneously, e.g., by subcutaneous injection.
41. The method of any one of the preceding embodiments, wherein the subject is a
- 10 human.
42. The method of any one of the preceding embodiments, wherein the subject is an adult (e.g., over the age of 18 years old).
- 15 43. The method of any one of the preceding embodiments, wherein the subject is a pediatric subject, e.g., a child (e.g., under the age of 18, 16, 14, 12, 10, 8, 6, or 4 years).
44. The method of any one of the preceding embodiments, wherein prior to administration of the MC4R agonist, the subject has previously received treatment for
- 20 obesity, e.g., a non-genetic obesity, e.g., hypothalamic obesity.
45. The method of any one of the preceding embodiments, wherein after a first administration of the MC4R agonist (e.g., at least 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 4 months, 5 months, 6 months, 8 months, 10 months, 1 year, or longer), the
- 25 subject exhibits a reduction in BMI.
46. The method of embodiment 45, wherein the reduction of BMI in the subject is greater than 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14% 16%, 18%, 20%, or more, e.g., relative to a reference standard (e.g., BMI prior to
- 30 administration of the MC4R agonist).

47. The method of any one of embodiments 45-46, wherein the reduction of BMI in the subject is greater than 0.5%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).
- 5 48. The method of any one of embodiments 45-47, wherein the reduction of BMI in the subject is greater than 5%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).
49. The method of any one of embodiments 45-47, wherein the reduction of BMI in the
10 subject is greater than 10%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).
50. The method of any one of embodiments 45-46, wherein the reduction of BMI in the subject is between 1%-10% (e.g., 1-5%, or 5-10%), e.g., relative to a reference standard (e.g.,
15 BMI prior to administration of the MC4R agonist).
51. The method of any one of embodiments 45-50, wherein the reduction of BMI in the subject occurs between 8 weeks and 6 months after administration of the MC4R agonist.
- 20 52. The method of any one of the preceding embodiments, wherein the subject is administered an additional agent (e.g., an additional therapeutic agent).
53. The method of any of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (I-a):
25
$$\text{H-A}^1\text{-c(A}^2\text{-A}^3\text{-A}^4\text{-A}^5\text{-A}^6\text{-A}^7\text{-A}^8\text{-A}^9\text{)-A}^{10}\text{-NH}_2 \quad (\text{I-a})$$

or a pharmaceutically acceptable salt thereof, wherein:
A¹ is Phe, D-Phe, or Nle;
A² is Cys;
A³ is deleted;
30 A⁴ is His;
A⁵ is D-Phe or D-(Et)Tyr;

A⁶ is Arg or hArg;

A⁷ is Trp or Bip;

A⁸ is Ala, β-Ala, Gaba, or Apn;

A⁹ is D-Cys; and

5 A¹⁰ is Thr or deleted.

54. The method of embodiment 53, wherein the MC4R agonist of Formula (I-a) is selected from:

(SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH₂;

10 (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH₂;

(SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH₂;

15 (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂;

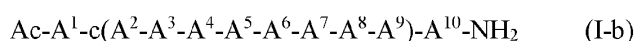
(SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂;

(SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂; and

(SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂.

20

55. The method of any of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (I-b):



or a pharmaceutically acceptable salt thereof, wherein:

25 A¹ is Nle, A6c, D-2-Nal, Cha, Oic, Chg, hCha, D-Cha, D-hCha, Nip, hPro, hLeu, Phe, D-Phe, D-Chg, hPhe, β-hMet, Gaba, Leu, Ile, Val, 2-Nal, Arg or D-Arg;

A² is Asp, Cys, D-Cys, or Pen;

A³ is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, D-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, deleted;

30 A⁴ His or 3-Pal;

A⁵ is Phe, D-Phe, or D-2-Nal;

A⁶ is Arg;

A⁷ is Trp, 1-Nal, 2-Nal, Bal, or D-Trp;

A⁸ is β -Ala, A6c, Ahx, Apn, Gaba, Ala, Aha, D-Ala or deleted;

A⁹ is Lys, Cys, D-Cys, or Pen;

5 A¹⁰ is deleted.

wherein A² and A⁹ are pairwise selected to form a disulfide or lactam bridge.

56. The method of embodiment 55, wherein the MC4R agonist of Formluea (I-b) is selected from:

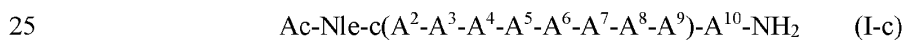
- 10 (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp- β -Ala-Lys)-NH₂;
- (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH₂;
- (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH₂;
- (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;
- (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH₂;
- 15 (SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- 20 (SEQ ID NO: 14) Ac-Nle-c(Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- 25 (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 20) Ac-Nle-c(D-Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
- 30 (SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
- (SEQ ID NO: 25) Ac-Nle-c(Cys- β -Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;

- (SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
5 (SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
10 (SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
15 (SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
20 (SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
25 (SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH₂;
30 (SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH₂;

- (SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH₂;
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH₂;
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH₂;
5 (SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH₂;
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH₂;
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH₂;
10 (SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH₂;
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH₂;
15 (SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH₂;
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH₂;
20 (SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH₂;
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH₂;
25 (SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
30 (SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;

- (SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 5 (SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH₂;
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH₂;
 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH₂;
 10 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH₂;
 (SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
 (SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
 (SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 15 (SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 20 (SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂; and
 (SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂.

57. The method of any of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (I-c):



or a pharmaceutically acceptable salt thereof, wherein:

A² is Asp, Cys, D-Cys, or Pen;

A³ is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, Aib, DI-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, or deleted;

30 A⁴ is His or 3-Pal;

A⁵ is D-Phe, D-2-Nal, or Phe;

A⁶ is Arg;

A⁷ is Trp, D-Trp, 2-Nal, 1-Nal, Bal;

A⁸ is β -Ala, A6c, Ahx, Apn, Gaba, D-Ala, Aha, Ala or deleted;

A⁹ is Lys, Cys, D-Cys or Pen; and

5 A¹⁰ is deleted,

wherein A² and A⁹ are pairwise selected to form a disulfide or lactam bridge.

58. The method of embodiment 58, wherein the MC4R agonist of Formula (I-c) is selected from:

- 10 (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp- β -Ala-Lys)-NH₂;
(SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH₂;
(SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH₂;
(SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;
(SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH₂;
15 (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 14) Ac-Nle-c(Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
20 (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 20) Ac-Nle-c(D-Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
25 (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 25) Ac-Nle-c(Cys- β -Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
30 (SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH₂;

- (SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
5 (SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH₂;
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH₂;
10 (SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH₂;
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH₂;
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH₂;
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH₂;
15 (SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH₂;
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH₂;
20 (SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH₂;
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH₂;
25 (SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH₂;
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH₂;
30 (SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂;

- (SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH₂;
 5 (SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
 10 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH₂;
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH₂;
 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH₂; and
 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH₂.
- 15 59. The method of any of the preceding claims, wherein the MC4R agonist is a compound of Formula (I-d):
- $$\text{H-D-Phe-c(A}^2\text{-A}^3\text{-A}^4\text{-A}^5\text{-A}^6\text{-A}^7\text{-A}^8\text{-A}^9\text{)-A}^{10}\text{-NH}_2 \quad (\text{I-d})$$
- or a pharmaceutically acceptable salt thereof, wherein:
- A² is Cys;
- 20 A³ is deleted;
- A⁴ is His;
- A⁵ is D-Phe or D-(Et)Tyr;
- A⁶ is Arg or hArg;
- A⁷ is Trp or Bip;
- 25 A⁸ is Ala, β-Ala, or Gaba;
- A⁹ is D-Cys; and
- A¹⁰ is Thr.
60. The method of embodiment 60, wherein the MC4R agonist of Formula (I-d) is selected
- 30 from:
- (SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH₂;

- (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH₂;
 5 (SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂; and
 (SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH₂.
- 10 61. The method of any of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-a):
- $$\text{H-Yyy-c(Aaa-Xxx-D-Phe-Arg-Trp-Bbb)-NH}_2 \quad (\text{XII-a})$$
- or a pharmaceutically acceptable salt thereof, wherein:
 Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or
 15 Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;
 Xxx is Asn, Gln, Ser, Thr; and
 Yyy is Lys, Arg, D-Lys, D-Arg.
62. The method embodiment 61, wherein the MC4R agonist of Formula (XII-a) is
 20 selected from:
- (SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 25 (SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 30 (SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

- (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and
 5 (SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

63. The method of any of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-b):



- 10 or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or
 Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;
 Xxx is Asn, Gln, Ser, Thr; and
 Yyy is Lys, Arg, D-Lys, D-Arg.

15

64. The method of embodiment 63, wherein the MC4R agonist of Formula (XII-b) is selected from:

- (SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 20 (SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH₂;
 (SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 25 (SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 30 (SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and
 (SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

5

65. The method of any of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-c):



or a pharmaceutically acceptable salt thereof, wherein:

10 A₁ is H or Ac;

A₂ is OH or NH₂;

Yyy is L-Arg or D-Arg;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or

15 Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and

Xxx is Asn, Gln, Ser, or Thr.

66. The method of embodiment 65, wherein the MC4R agonist of Formula (XII-c) is selected from:

20 (SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH₂;

25 (SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

30 (SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

- (SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 5 (SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 10 (SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
 15 (SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 20 (SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH; and
 (SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH.

67. The method of any of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-d):



or a pharmaceutically acceptable salt thereof, wherein:

A_1 is H or Ac;

A_2 is OH or NH₂;

Y_{yy} is L-Lys or D-Lys;

- 30 Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and
Xxx is Asn, Gln, Ser, or Thr.

68. The method of embodiment 67, wherein the MC4R agonist of Formula (XII-d) is
5 selected from:
- (SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
10 (SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
15 (SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
20 (SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
25 (SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
30 (SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
5 (SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂, and
(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

69. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI of between about 5-10, e.g., after
10 16 weeks relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist.

70. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI of between 5-10, e.g., after 16
15 weeks relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist, wherein the subject is a pediatric subject between 6 to less than 18 years of age.

71. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI of between about 1-5, e.g., after
20 16 weeks relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist, wherein the subject is an adult subject equal to or greater than 18 years of age.

25 72. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI between about 15-20%, e.g., after 16 weeks relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist.

30 73. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI Z-Score between about 1-5, e.g.,

after 16 weeks relative to the baseline BMI Z-Score, e.g., the BMI Z-Score of the subject prior to administration of the MC4R agonist.

74. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight between about 10-20 kg, e.g., after 16 weeks relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist.

75. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight between about 15-20 kg, e.g., after 16 weeks relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist, wherein the subject is a pediatric subject between 6 to less than 18 years of age.

76. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight between about 5-10 kg, e.g., after 16 weeks relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist, wherein the subject is an adult subject equal to or greater than 18 years of age.

77. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight between about 10-20%, e.g., after 16 weeks relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist.

78. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight of between 15-20%, e.g., after 16 weeks relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist, wherein the subject is a pediatric subject between 6 to less than 18 years of age.

79. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight of between about 5-10%, e.g., after 16 weeks relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist, wherein the subject is an adult subject equal to or
5 greater than 18 years of age.

80. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in the weekly average of the daily most hunger score of between about 1-5, e.g., after 16 weeks relative to the baseline weekly
10 average of the daily most hunger score, e.g., the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist.

81. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI of between about 1-10, e.g., after
15 16 weeks relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist.

82. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI of between 12-20%, e.g., after 16
20 weeks relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist.

83. The method of any of the preceding embodiments, wherein after administration of the MC4R agonist, the subject experiences a reduction in the weekly average of the daily most
25 hunger score of between about 1-5, e.g., after 16 weeks relative to the baseline weekly average of the daily most hunger score, e.g., the weekly average of the daily most hunger score of the subject prior to administration of the MC4R agonist.

84. The method of any of the preceding embodiments, the method comprising
30 administering to the subject a compound of Formula I (e.g., Formula (I), (I-a), (I-b), (I-c), and (I-d)) or Formula XII (e.g., Formula (XII) (Formula (XII), (XII-a), (XII-b), (XII-c), and

(XII-d)), wherein upon administration of Formula I or Formula XII, the subject experiences one or more of:

- (i) a BMI reduction $\geq 5\%$ after 16 weeks from baseline for all subjects;
- (ii) a mean reduction in BMI $\geq 10\%$ after 16 weeks from baseline for a subject completing the course of therapy;
- (iii) a mean reduction in BMI of between 5-10, e.g., after 16 weeks from baseline;
- (iv) a mean reduction in BMI of between 6-8, e.g., after 16 weeks from baseline;
- (v) a mean reduction in BMI of between 2-5, e.g., after 16 weeks from baseline;
- (vi) a mean percentage reduction in BMI of between about 15-20%, after 16 weeks from baseline;
- (vii) a mean reduction in BMI Z-Score of between 1-5, e.g., after 16 weeks from baseline;
- (viii) a mean reduction in weight of between about 12-20 kg, e.g., after 16 weeks from baseline;
- (ix) a mean reduction in weight of between about 15-20 kg, e.g., after 16 weeks from baseline;
- (x) a mean reduction in weight of between 5-10 kg, e.g., after 16 weeks from baseline;
- (xi) a mean percentage reduction in weight of between 10-20%, e.g., after 16 weeks from baseline;
- (xii) a mean percentage reduction in weight of between 15-20%, e.g., after 16 weeks from baseline;
- (xiii) a mean percentage reduction in weight of between 5-10%, e.g., after 16 weeks from baseline; and
- (xiv) a mean reduction in the weekly average of the daily most hunger score of between 1-4, e.g., after 16 weeks from baseline.

85. The method of embodiment 84, comprising (i).

30 86. The method of embodiment 84, comprising (ii).

87. The method of embodiment 84, comprising (iii).
88. The method of embodiment 84, comprising (iv).
- 5 89. The method of embodiment 84, comprising (v).
90. The method of embodiment 84, comprising (vi).
91. The method of embodiment 84, comprising (vii).
- 10 92. The method of embodiment 84, comprising (viii).
93. The method of embodiment 84, comprising (ix).
- 15 94. The method of embodiment 84, comprising (x).
95. The method of embodiment 84, comprising (xi).
96. The method of embodiment 84, comprising (xii).
- 20 97. The method of embodiment 84, comprising (xiii).
98. The method of embodiment 84, comprising (xiv).
- 25 99. The method of embodiment 84, comprising (i) and (ii).
100. The method of embodiment 84, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric subject, e.g., less than 18 years of age.
- 30 101. The method of embodiment 84, comprising (v), (x), and (xiii), wherein the subject is an adult.

102. The method of embodiment 84, wherein the compound is a compound of Formula (I) (e.g., Formula (I-a), Formula (I-b), Formula (I-c), and Formula (I-d).

- 5 103. The method of embodiment 102, comprising (i).
104. The method of embodiment 102, comprising (ii).
105. The method of embodiment 102, comprising (iii).
- 10 106. The method of embodiment 102, comprising (iv).
107. The method of embodiment 102, comprising (v).
- 15 108. The method of embodiment 102, comprising (vi).
109. The method of embodiment 102, comprising (vii).
110. The method of embodiment 102, comprising (viii).
- 20 111. The method of embodiment 102, comprising (ix).
112. The method of embodiment 102, comprising (x).
- 25 113. The method of embodiment 102, comprising (xi).
114. The method of embodiment 102, comprising (xii).
115. The method of embodiment 102, comprising (xiii).
- 30 116. The method of embodiment 102, comprising (xiv).

117. The method of embodiment 102, comprising (i) and (ii).
118. The method of embodiment 102, comprising (iv), (vii), (ix), and (xii), wherein the
5 subject is a pediatric subject, e.g., less than 18 years of age.
119. The method of embodiment 102, comprising (v), (x), and (xiii), wherein the subject is
an adult.
- 10 120. The method of embodiment 84, wherein the compound is a compound of Formula (I-
a).
121. The method of compound 120, comprising (i).
- 15 122. The method of compound 120, comprising (ii).
123. The method of compound 120, comprising (iii).
124. The method of embodiment 120, comprising (iv).
20
125. The method of embodiment 120, comprising (v).
126. The method of embodiment 120, comprising (vi).
- 25 127. The method of embodiment 120, comprising (vii).
128. The method of embodiment 120, comprising (viii).
129. The method of embodiment 120, comprising (ix).
30
130. The method of embodiment 120, comprising (x).

131. The method of embodiment 120, comprising (xi).
132. The method of embodiment 120, comprising (xii).
- 5 133. The method of embodiment 120, comprising (xiii).
134. The method of embodiment 120, comprising (xiv).
- 10 135. The method of embodiment 120, comprising (i) and (ii).
136. The method of embodiment 120, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric subject, e.g., a subject less than 18 years of age.
- 15 137. The method of embodiment 120, comprising (v), (x), and (xiii), wherein the subject is an adult.
138. The method of embodiment 84, wherein the compound is a compound of Formula (I-b).
- 20 139. The method of compound 138, comprising (i).
140. The method of compound 138, comprising (ii).
- 25 141. The method of compound 138, comprising (iii).
142. The method of embodiment 138, comprising (iv).
143. The method of embodiment 138, comprising (v).
- 30 144. The method of embodiment 138, comprising (vi).

145. The method of embodiment 138, comprising (vii).
146. The method of embodiment 138, comprising (viii).
- 5 147. The method of embodiment 138, comprising (ix).
148. The method of embodiment 138, comprising (x).
- 10 149. The method of embodiment 138, comprising (xi).
150. The method of embodiment 138, comprising (xii).
151. The method of embodiment 138, comprising (xiii).
- 15 152. The method of embodiment 138, comprising (xiv).
153. The method of embodiment 138, comprising (i) and (ii).
- 20 154. The method of embodiment 138, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric patient between 6 to less than 18 years of age.
155. The method of embodiment 138, comprising (v), (x), and (xiii), wherein the subject is an adult.
- 25 156. The method of embodiment 84, wherein the compound is a compound of Formula (I-c).
157. The method of compound 156, comprising (i).
- 30 158. The method of compound 156, comprising (ii).

159. The method of compound 156, comprising (iii).
160. The method of embodiment 156, comprising (iv).
- 5 161. The method of embodiment 156, comprising (v).
162. The method of embodiment 156, comprising (vi).
- 10 163. The method of embodiment 156, comprising (vii).
164. The method of embodiment 156, comprising (viii).
165. The method of embodiment 156, comprising (ix).
- 15 166. The method of embodiment 156, comprising (x).
167. The method of embodiment 156, comprising (xi).
- 20 168. The method of embodiment 156, comprising (xii).
169. The method of embodiment 156, comprising (xiii).
170. The method of embodiment 156, comprising (xiv).
- 25 171. The method of embodiment 156, comprising (i) and (ii).
172. The method of embodiment 156, comprising (iv), (vii), (ix), and (xii), wherein the
subject is a pediatric patient between 6 to less than 18 years of age.
- 30

173. The method of embodiment 156, comprising (v), (x), and (xiii), wherein the subject is an adult subject equal to or greater than 18 years of age.

5 174. The method of embodiment 84, wherein the compound is a compound of Formula (I-d).

175. The method of compound 174, comprising (i).

10 176. The method of compound 174, comprising (ii).

177. The method of compound 174, comprising (iii).

15 178. The method of embodiment 174, comprising (iv).

179. The method of embodiment 174, comprising (v).

180. The method of embodiment 174, comprising (vi).

20 181. The method of embodiment 174, comprising (vii).

182. The method of embodiment 174, comprising (viii).

25 183. The method of embodiment 174, comprising (ix).

184. The method of embodiment 174, comprising (x).

185. The method of embodiment 174, comprising (xi).

30 186. The method of embodiment 174, comprising (xii).

187. The method of embodiment 174, comprising (xiii).
188. The method of embodiment 174, comprising (xiv).
- 5 189. The method of embodiment 174, comprising (i) and (ii).
190. The method of embodiment 174, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric patient between 6 to less than 18 years of age.
- 10 191. The method of embodiment 174, comprising (v), (x), and (xiii), wherein the subject is an adult subject equal to or greater than 18 years of age.
192. The method of embodiment 84, wherein the compound is represented by the following structural formula:
- 15 Arg-c(Cys-D-Ala-Hia-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140)
193. The method of compound 192, comprising (i).
194. The method of compound 192, comprising (ii).
- 20 195. The method of compound 192, comprising (iii).
196. The method of embodiment 192, comprising (iv).
- 25 197. The method of embodiment 192, comprising (v).
198. The method of embodiment 192, comprising (vi).
199. The method of embodiment 192, comprising (vii).
- 30 200. The method of embodiment 192, comprising (viii).

201. The method of embodiment 192, comprising (ix).
202. The method of embodiment 192, comprising (x).
- 5 203. The method of embodiment 192, comprising (xi).
204. The method of embodiment 192, comprising (xii).
- 10 205. The method of embodiment 192, comprising (xiii).
206. The method of embodiment 192, comprising (xiv).
207. The method of embodiment 192, comprising (i) and (ii).
- 15 208. The method of embodiment 192, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric patient between 6 to less than 18 years of age.
209. The method of embodiment 192, comprising (v), (x), and (xiii), wherein the subject is
- 20 an adult subject equal to or greater than 18 years of age.
210. The method of embodiment 84, wherein the compound is a compound of Formula (XII).
- 25 211. The method of compound 210, comprising (i).
212. The method of compound 210, comprising (ii).
213. The method of compound 210, comprising (iii).
- 30 214. The method of embodiment 210, comprising (iv).

215. The method of embodiment 210, comprising (v).
216. The method of embodiment 210, comprising (vi).
- 5 217. The method of embodiment 210, comprising (vii).
218. The method of embodiment 210, comprising (viii).
- 10 219. The method of embodiment 210, comprising (ix).
220. The method of embodiment 210, comprising (x).
221. The method of embodiment 210, comprising (xi).
- 15 222. The method of embodiment 210, comprising (xii).
223. The method of embodiment 210, comprising (xiii).
- 20 224. The method of embodiment 210, comprising (xiv).
225. The method of embodiment 210, comprising (i) and (ii).
226. The method of embodiment 210, comprising (iv), (vii), (ix), and (xii), wherein the
25 subject is a pediatric patient between 6 to less than 18 years of age.
227. The method of embodiment 210, comprising (v), (x), and (xiii), wherein the subject is
an adult subject equal to or greater than 18 years of age.
- 30 228. The method of embodiment 84, wherein the compound is a compound of Formula
(XII-a).

229. The method of compound 228, comprising (i).
230. The method of compound 228, comprising (ii).
- 5 231. The method of compound 228, comprising (iii).
232. The method of embodiment 228, comprising (iv).
- 10 233. The method of embodiment 228, comprising (v).
234. The method of embodiment 228, comprising (vi).
235. The method of embodiment 228, comprising (vii).
- 15 236. The method of embodiment 228, comprising (viii).
237. The method of embodiment 228, comprising (ix).
- 20 238. The method of embodiment 228, comprising (x).
239. The method of embodiment 228, comprising (xi).
240. The method of embodiment 228, comprising (xii).
- 25 241. The method of embodiment 228, comprising (xiii).
242. The method of embodiment 228, comprising (xiv).
- 30 243. The method of embodiment 228, comprising (i) and (ii).

244. The method of embodiment 228, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric patient between 6 to less than 18 years of age.

245. The method of embodiment 228, comprising (v), (x), and (xiii), wherein the subject is
5 an adult subject equal to or greater than 18 years of age.

246. The method of embodiment 84, wherein the compound is a compound of Formula (XII-b).

10 247. The method of compound 246, comprising (i).

248. The method of compound 246, comprising (ii).

249. The method of compound 246, comprising (iii).
15

250. The method of embodiment 246, comprising (iv).

251. The method of embodiment 246, comprising (v).

20 252. The method of embodiment 246, comprising (vi).

253. The method of embodiment 246, comprising (vii).

254. The method of embodiment 246, comprising (viii).
25

255. The method of embodiment 246, comprising (ix).

256. The method of embodiment 246, comprising (x).

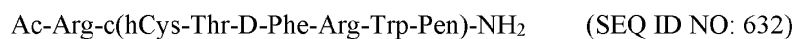
30 257. The method of embodiment 246, comprising (xi).

258. The method of embodiment 246, comprising (xii).
259. The method of embodiment 246 comprising (xiii).
- 5 260. The method of embodiment 246, comprising (xiv).
261. The method of embodiment 246, comprising (i) and (ii).
262. The method of embodiment 246, comprising (iv), (vii), (ix), and (xii), wherein the
10 subject is a pediatric patient between 6 to less than 18 years of age.
263. The method of embodiment 246, comprising (v), (x), and (xiii), wherein the subject is
an adult subject equal to or greater than 18 years of age.
- 15 264. The method of embodiment 84, wherein the compound is a compound of Formula
(XII-c).
265. The method of compound 264, comprising (i).
- 20 266. The method of compound 264, comprising (ii).
267. The method of compound 264, comprising (iii).
268. The method of embodiment 264, comprising (iv).
- 25 269. The method of embodiment 264, comprising (v).
270. The method of embodiment 264, comprising (vi).
- 30 271. The method of embodiment 264, comprising (vii).

272. The method of embodiment 264, comprising (viii).
273. The method of embodiment 264, comprising (ix).
- 5 274. The method of embodiment 264, comprising (x).
275. The method of embodiment 264, comprising (xi).
276. The method of embodiment 264, comprising (xii).
- 10 277. The method of embodiment 264 comprising (xiii).
278. The method of embodiment 264, comprising (xiv).
- 15 279. The method of embodiment 264, comprising (i) and (ii).
280. The method of embodiment 264, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric patient between 6 to less than 18 years of age.
- 20 281. The method of embodiment 264, comprising (v), (x), and (xiii), wherein the subject is an adult subject equal to or greater than 18 years of age.
282. The method of embodiment 84, wherein the compound is a compound of Formula (XII-d).
- 25 283. The method of compound 282, comprising (i).
284. The method of compound 282, comprising (ii).
- 30 285. The method of compound 282, comprising (iii).

286. The method of embodiment 282, comprising (iv).
287. The method of embodiment 282, comprising (v).
- 5 288. The method of embodiment 282, comprising (vi).
289. The method of embodiment 282, comprising (vii).
290. The method of embodiment 282, comprising (viii).
- 10 291. The method of embodiment 282, comprising (ix).
292. The method of embodiment 282, comprising (x).
- 15 293. The method of embodiment 282, comprising (xi).
294. The method of embodiment 282, comprising (xii).
295. The method of embodiment 282, comprising (xiii).
- 20 296. The method of embodiment 282, comprising (xiv).
297. The method of embodiment 282, comprising (i) and (ii).
- 25 298. The method of embodiment 282, comprising (iv), (vii), (ix), and (xii), wherein the subject is a pediatric patient between 6 to less than 18 years of age.
299. The method of embodiment 282, comprising (v), (x), and (xiii), wherein the subject is an adult subject equal to or greater than 18 years of age.
- 30

300. The method of embodiment 84, wherein the compound is represented by the structural formula:



- 5 301. The method of compound 300, comprising (i).
302. The method of compound 300, comprising (ii).
303. The method of compound 300, comprising (iii).
- 10 304. The method of embodiment 300, comprising (iv).
305. The method of embodiment 300, comprising (v).
- 15 306. The method of embodiment 300, comprising (vi).
307. The method of embodiment 300, comprising (vii).
308. The method of embodiment 300, comprising (viii).
- 20 309. The method of embodiment 300, comprising (ix).
310. The method of embodiment 300, comprising (x).
- 25 311. The method of embodiment 300, comprising (xi).
312. The method of embodiment 300, comprising (xii).
313. The method of embodiment 300, comprising (xiii).
- 30 314. The method of embodiment 300, comprising (xiv).

315. The method of embodiment 300, comprising (i) and (ii).

316. The method of embodiment 300, comprising (iv), (vii), (ix), and (xii), wherein the
5 subject is a pediatric patient between 6 to less than 18 years of age.

317. The method of embodiment 300, comprising (v), (x), and (xiii), wherein the subject is
an adult subject equal to or greater than 18 years of age.

10

EXAMPLES

Example 1: An open-label study to evaluate the safety and efficacy of an exemplary MC4R agonist in subjects with hypothalamic obesity

15 Purpose

This example describes a phase 2 study that seeks to evaluate the change in body
weight in response to an exemplary MC4R agonist, e.g., setmelanotide (i.e., SEQ ID NO:
140) administered subcutaneously (SC) daily in patients with hypothalamic obesity (HO).
Additional objectives of this study include evaluation of changes in parameters of body
20 weight, body mass index (BMI), waist circumference, and hunger in response to
setmelanotide in patients with HO and to evaluate the safety and tolerability of setmelanotide
in patients with HO. In addition, this study seeks to evaluate changes in weight and BMI in
patients of different age groups and changes in metabolic parameters following treatment
with setmelanotide.

25 Investigational Study Drug

Setmelanotide, 10 mg/mL in a sterile solution for injection, was provided at 1.0, 2.0, 3.0 mg
QD for patients 6 to <16 years of age, and 2.0 to 3.0 mg QD for patients $\geq$ 16 years of age.

Primary Endpoints

The primary endpoint of this study was to identify a proportion of patients with $\geq$ 5%
30 reduction from baseline in BMI after 16 weeks of setmelanotide treatment compared to a
historic control of <5% in this patient population.

Secondary Endpoints

The secondary endpoints included determination of:

- Composite proportion of patients aged ≥ 6 to < 18 years with ≥ 0.2 reduction of BMI Z-score and patients aged ≥ 18 years with 5% reduction of body weight from baseline after 16 weeks of setmelanotide
- Proportion of patients aged ≥ 6 to < 18 years with ≥ 0.2 reduction of BMI Z-score from baseline after 16 weeks of setmelanotide
- Proportion of patients aged ≥ 18 years with $\geq 5\%$ reduction of body weight from baseline after 16 weeks of setmelanotide
- Change from baseline in waist circumference in patients aged ≥ 18 years after 16 weeks of setmelanotide treatment.
- Change in hunger in response to 16 weeks of setmelanotide treatment as measured by change from baseline in daily and global hunger scores.
- Safety and tolerability assessed by the frequency and severity of AEs, vital signs, and laboratory evaluations.
- Change from baseline in metabolic parameters following treatment with setmelanotide, including fasting glucose, HbA1c, lipid profiles (total-, high-density lipoprotein [HDL]-, and low-density lipoprotein [LDL]-cholesterol, triglycerides).
- Proportion of patients, regardless of age, with $\geq 5\%$ body weight loss from baseline after 16 weeks of setmelanotide treatment compared to a historic control of $< 5\%$ in this patient population.
- Change from baseline in BMI, weight, and waist circumference, regardless of age, after 16 weeks of setmelanotide treatment.
- Change from baseline in BMI Z-score in patients aged 6 to 12 years and in those aged 6 to < 18 years.

Study Design Rationale

This study describes a Phase 2, multicenter, open-label, proof of concept study designed to assess the effect of setmelanotide on weight loss within a population affected by HO. Approximately 15 patients aged 6 to 40 years, inclusive, were enrolled across approximately 3-5 clinical sites in the United States (US). Setmelanotide was evaluated as a potential treatment for obesity in rare mechanistically induced populations with hypothalamic

injury and subsequent obesity. The open-label design was supported by the compelling efficacy results from earlier pivotal studies in patients with POMC and LEPR deficiency obesity that demonstrate that setmelanotide induces rapid and sustained significant and clinically meaningful weight loss accompanied by statistically significant and clinically meaningful reduction in hunger in these patient populations.

Screening Period

Upon providing informed consent, patients entered the Screening Period, during which they were assessed for eligibility and complete all screening procedures.

Treatment Period

- 10 Patients who were determined to be eligible, based on Screening assessments, returned to the clinic for the Baseline Visit (Visit 2) and received the first setmelanotide dose. The starting setmelanotide dose was dependent on patient age; however, for all patients, the setmelanotide dose was titrated to a final dose of 3.0 mg/day (initial titration phase), as follows

Patients aged 6 to <16 years, inclusive

- 15 • Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients received setmelanotide 1.0 mg/day.
• Starting at approximately Day 15 through 28, patients received setmelanotide 2.0 mg/day.

Patients/caregivers were contacted by study center personnel on Day 15 to ensure dose titration occurred and to document any AEs.

- 20 • Starting on approximately Day 29 (Visit 3), patients received setmelanotide 3.0 mg/day; patients continued to receive setmelanotide 3.0 mg/day for 12 weeks.

Patients aged ≥16 years, inclusive

- 25 • Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients received setmelanotide 2.0 mg/day.
• Starting at approximately Day 15, patients received setmelanotide 3.0 mg/day; patients continue to receive setmelanotide 3.0 mg/day for 14 weeks.

Patients/caregivers were contacted by study center personnel on Day 15 to ensure dose titration occurred and to document any adverse events.

- 30 Patients returned to the study center for Visits 3, 4, and 5 (Weeks 4, 8, and 12, respectively), with each of these visits conducted approximately 4 weeks apart. All patients returned to the

study center at Week 16 (Visit 6) and received the last setmelanotide injection. Study endpoints were analyzed at Visit 6. After completion of Visit 6, participation in the current study then concluded in one of the following 2 ways:

- Patients meeting the primary endpoint were eligible to be enrolled in a separate extension study under which auspices the patient continued to receive setmelanotide.
- Patients who did not meet the primary endpoint or elected not to continue setmelanotide discontinued setmelanotide at Visit 6 and return for an End-of-Study (EOS) Visit (Visit 7) 4 weeks thereafter for a final safety review under the auspices of the current study

10 Inclusion Criteria

Patients met the following criteria to be eligible for study participation:

1. Patient has documented evidence of HO, including:
 - a. Recent (within the previous 8 months before Screening) evidence of hypothalamic injury on magnetic resonance imaging (MRI); and
 - 15 b. Diagnosis of craniopharyngioma or other non-malignant brain tumor affecting the hypothalamic region; and
 - c. Has undergone surgery, or chemotherapy, or radiation ≥ 6 months and ≤ 15 years before screening.
2. Patient has either unilateral hypothalamic lesions (at least 6 patients) or bilateral hypothalamic lesions (at least 7 patients), as assessed by MRI.
- 20 3. Aged 6 to 40 years, inclusive, at time of enrollment.
4. Obesity, documented by a BMI ≥ 35 kg/m² for patients ≥ 18 years of age or BMI ≥ 95 th percentile for age and gender for patients 6 to < 18 years of age based on the US Centers for Disease Control and Prevention criteria.
- 25 5. Documented increase in BMI (change from pre-surgery baseline in BMI Z-score ≥ 0.2 for patients < 18 years of age or BMI $> 5\%$ for patients ≥ 18 years of age) either during the first 6 months following surgery or within 1 year before surgery and still present at Screening.
6. More than 6 months after the end of post-tumor treatment, including chemotherapy, surgery, or radiation.
- 30 7. Patient met one of the following contraception requirements:
 - If a female of childbearing potential, defined as fertile, following menarche and until

becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must use a highly effective form of contraception.

- If a female of non-childbearing potential, defined as permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or post-menopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone [FSH] level in the post-menopausal laboratory range), contraception is not required during the study.
 - Younger female patients who have not reached menarche upon study entry will be assessed for Tanner staging and at first menarche will be required to comply with contraception requirements and pregnancy testing as outlined in the protocol.
 - If a male with female partner(s) of childbearing potential, must agree to a double barrier method if they become sexually active during the study. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the study.
8. Ability to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and sign the written informed consent, or, for patients aged <18 years, a parent/legal guardian that can sign.
9. If receiving hormone replacement therapy (ie, thyroid hormones, glucocorticoids, growth hormone or other medications known to affect metabolism or weight/body composition), the dose of such therapy has remained stable for at least 2 months prior to Screening.

Exclusion Criteria

Patients meeting any of the following criteria were not eligible for study participation:

1. Weight gain >5% in the previous 3 months.
 2. Weight loss $\geq$ 2% in the previous 3 months.
- Note:* Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.) were allowed if:
- the regimen and/or dose has been stable for at least 3 months prior to randomization
 - the patient has not experienced weight loss $\geq$ 2% during the previous 3 months, and
 - the patient intends to keep the regimen and/or dose stable throughout the course of the

study.

3. Bariatric surgery or procedure (eg, gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc) within the last 6 months. All patients with a history of bariatric surgery or procedures must be discussed with and receive approval from the Sponsor prior to enrollment.
4. Diagnosis of severe psychiatric disorders (eg, schizophrenia, bipolar disorder, personality disorder), or Major Depressive Disorder (MDD) within the previous 2 years, or Screening Patient Health Questionnaire (PHQ)-9/PHQ-A score ≥ 15 , or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month.
5. Glycated hemoglobin (HbA1c) $>10.0\%$ at Screening.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. Glomerular filtration rate (GFR) <30 mL/min/1.73 m² during Screening.
8. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for study participation.
9. History or close family history (parents or siblings) of skin cancer or melanoma (not including noninvasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
10. Participation in any clinical study with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first setmelanotide dose.
11. Previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
12. Inability to comply with once daily (QD) injection regimen.
13. Pregnant and/or breastfeeding or desiring to become pregnant during this trial.

14. Cognitive impairment that, in the Investigator's opinion, precludes participation to the study and completions of study procedures or questionnaires.

15. Patient is, in Investigator's opinion, otherwise not suitable to participate in the study.

Duration of Treatment

- 5 All patients received study treatment for 16 weeks. Total study participation lasted between 22 and 28 weeks, based on the variable length of the Screening Period

Treatment

All patients received open-label setmelanotide in this study. Setmelanotide was provided as a preserved, multidose solution for injection to be administered SC, QD. It was formulated as a

- 10 10 mg/mL sterile, preserved, clear to slightly opalescent, colorless to slightly colored solution, practically free of visible particles. The drug product solution (1 mL) was presented in a clear 2R glass vial with a rubber stopper. Packaging and labeling met all regulatory requirements. Setmelanotide was administered as SC injection QD.

- 15 All patients received setmelanotide in this study. The starting setmelanotide dose was dependent on patient age at the time of Visit 2 (Day 1); however, for all patients, the setmelanotide dose was titrated to a final dose of 3.0 mg/day (initial titration phase), as follows:

Patients aged 6 to <16 years

- Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients received
20 setmelanotide 1.0 mg/day
- Starting at approximately Day 15 through 28, patients received setmelanotide 2.0 mg/day.
- Patients/caregivers were contacted by study center personnel on Day 15 to ensure dose titration occurred and to document any adverse events.
- 25 • Starting on approximately Day 29 (Visit 3), patients received setmelanotide 3.0 mg/day; patients continued to receive setmelanotide 3.0 mg/day for 12 weeks.

Patients aged ≥16 years

- Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients received setmelanotide 2.0 mg/day.
- 30 • Starting at approximately Day 15, patients received setmelanotide 3.0 mg/day; patients continued to receive setmelanotide 3.0 mg/day for 14 weeks.

Patient Assessments

All screening evaluations were completed and reviewed to confirm that potential patients meet all eligibility criteria. Exemplary evaluations included a medical history review, physical examination, comprehensive skin examination, measurement of height, weight, waist circumference, body composition assessment, pregnancy test (if applicable), daily hunger questionnaires, global hunger assessment, and evaluation of PHQ-A or PHQ-9, C-SSRS, SF-12 or SF-10, IWQOL, FSH, HbA1c, and fasting lipid panel. Adjustments were made depending upon specific circumstances and in consultation with the investigator. Immediate safety concerns were discussed immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Results

The results of the study showed that all patients achieved the primary endpoints of the study at 16 weeks on setmelanotide. Of the full analysis set (FAS) population (n=11), 100% of patients achieved the primary endpoint of greater than or equal to 5% reduction in BMI (p<0.0001). Of the completers (n=9), 100% of patients achieved at least a 10% reduction in BMI (p<0.0001). Further, setmelanotide treatment resulted in mean BMI reduction of -19.5% in 9 completers at 16 weeks, which translates to a -17.8% mean percent change in body weight after 16 weeks of setmelanotide (SD, 7.9%). Setmelanotide treatment resulted in statistically significant reduction in BMI Z score in all patients less than 18 years old. For the FAS set, this resulted in a -1.1 point mean change in BMI Z score after 16 weeks of setmelanotide treatment. The safety and tolerability of setmelanotide treatment was consistent with established data.

In addition to the reduction in BMI and BMI Z-Score across the full analysis set (FAS), there was a statistically significant and clinically meaningful reduction in weight for both pediatric and adult patients after 16 weeks of daily SC setmelanotide therapy as shown in Table 3 below.

Table 3. Summary of Weight (kg) Change from Baseline to 16 Weeks of Treatment by Age

Visit	Parameter	Statistic	6-<18 years (N =9)	≥18 years (N=2)	Total (N=11)
Baseline	Actual	N	9	2	11

Week 16		Mean (SD)	107.81 (29.91)	103.80 (3.68)	107.08 (26.83)
		90% CI	89.27, 126.36	87.38, 120.22	92.42, 121.75
		Median	119.23	103.80	110.40
		Min, Max	39.0, 141.4	101.2, 106.4	39.0, 141.4
	Actual	N	9	2	11
		Mean (SD)	89.98 (27.71)	96.78 (3.56)	91.22 (24.96)
		90% CI	72.80, 107.16	80.89, 112.67	77.58, 104.86
		Median	93.07	96.78	94.27
		Min, Max	25.4, 124.6	94.3, 99.3	25.4, 124.6
	Change from Baseline	N	9	2	11
		Mean (SD)	-17.83 (6.37)	-7.02 (0.12)	-15.87 (7.18)
		90% CI	-21.78, - 13.89	-7.54, -6.49	-19.79, - 11.94
		Median	-16.77	-7.02	-13.90
		Min, Max	-28.2, -9.5	-7.1, -6.9	-28.2, -6.9
	Percent Change from Baseline	N	9	2	11
		Mean (SD)	-17.80 (7.93)	-6.76 (0.13)	-15.79 (8.38)
		90% CI	-22.71, - 12.89	-7.32, -6.20	-20.37, - 11.21
		Median	-14.12	-6.76	-13.68
		Min, Max	-34.9, -10.7	-6.9, -6.7	-34.9, -6.7

The daily hunger questionnaire as assessed in patients ≥ 12 years of age also achieved a clinically meaningful diminution quantifying the most hungry the patient has experienced over the last 24 hours, with a mean reduction in the hunger score of -2.66 after 16 weeks.

- 5 This outcome exceeded what is typically established as a clinically meaningful change for

patients having a genetic defect in the MC4R pathway of 1-2 points, as shown in Table 4 below.

Table 4. Summary of Change from Baseline to Week 16 in the Weekly Average of the Daily
5 Most Hunger Scores in Patients ≥ 12 years of Age

	Visit	Parameter	Statistic	Total (N=8)
Most Hungry Last 24 hrs	Baseline	Actual	N	8
			Mean (SD)	7.18 (1.17)
			90% CI	6.40, 7.96
			Median	7.1
			Min, Max	5.4, 8.7
	Week 16	Actual	N	7
			Mean (SD)	4.55 (2.84)
			90% CI	2.47, 6.63
			Median	5.67
			Min, Max	1.0, 7.6
		Change from Baseline	N	7
			Mean (SD)	-2.66 (2.64)
			90% CI	-4.60, -0.72
			Median	-1.71
			Min, Max	-7.0, 0.4

Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

All eleven of the patients experienced at least one form of treatment emergent adverse event (TEAE), either related to administration or unrelated to administration. The most commonly
10 reported TEAE was nausea (63.6%). Skin hyperpigmentation, e.g., the development of a melanocytic naevus, was only reported in two of the eleven patients. A SAE related to *Clostridium difficile* colitis was classified as severe, but not related to setmelanotide therapy, and the patient was able to complete the study.

15 **Example 2: Long-Term Extension Study**

Purpose

This example describes a long-term extension study of the use of setmelanotide in treating hypothalamic obesity, and further to investigate the safety and tolerability of chronic setmelanotide administration for up to 5 years from initiation of treatment. Patients had the option to gain entry into the long-term extension study immediately after completion of a prior setmelanotide trial, having demonstrated satisfactory therapeutic efficacy and safety criteria to ensure there is no cessation in setmelanotide therapy.

Investigational Study Drug

Setmelanotide, 10 mg/mL in a sterile solution, QD. Dosing was continued at the dosage of the cessation of the previous setmelanotide trial, (e.g., 3.0 mg QD for most patients enrolled in the setmelanotide trial for treating subjects with hypothalamic obesity), unless a change is determined necessary by the Investigator, e.g., for safety, tolerability, TEAE, SAE, or other concern.

Primary Endpoint

The objective of this study was to examine the long-term safety parameters of chronic, daily subcutaneous setmelanotide injections for a period of up to 5 years. In order to assess this primary endpoint, the occurrence of TEAEs and SAEs were tracked, in addition to other clinical data including any new emergence of injection site reactions, changes in resting heart rate or blood pressure, laboratory workup (e.g., fasting glucose, HbA1c, lipid profiles (total-, high-density lipoprotein [HDL]-, and low-density lipoprotein [LDL]-cholesterol, triglycerides), liver enzymes, changes in physical examination (e.g., weight, BMI, BMI Z-Score), and cardiac changes (e.g., as measured by an electrocardiogram (ECG)).

Study Design Rationale

This study was a long-term, multi-center, open-label extension of several Phase 2 and 3 setmelanotide trials designed to investigate the safety and tolerability profile of chronic, daily SC setmelanotide administration for up to 5 years. All patients ≥ 2 years of age who previously participated in another setmelanotide clinical trial and have met efficacy and safety criteria were eligible to participate. Setmelanotide was being evaluated as a potential treatment for obesity caused by a myriad of etiologies, such as genetic and acquired defects in the MC4 receptor pathway. Previous trials have demonstrated that setmelanotide is useful in rapidly inducing weight loss and perception of hunger in subjects carrying mutations in the

POMC and LEPR genes located upstream of the MC4 receptor. Both weight loss and daily hunger scores were sustained and statistically significant and clinically meaningful over the course of the trial. Acquired defects encompass, e.g., hypothalamic obesity.

Treatment Period

- 5 All patients ≥ 2 years of age who have enrolled in a previous setmelanotide trial (e.g., the open-label study to evaluate the safety and efficacy of setmelanotide in subjects with hypothalamic obesity) and achieved therapeutic efficacy and safety criteria consistent with continuation of setmelanotide treatment as assessed by the Investigator are eligible to continue with their current setmelanotide treatment regimens for up to a 5-year duration of
- 10 the study period.

Eligibility Criteria

Patients met the following criteria to be eligible for study participation:

1. Patients ≥ 2 years of age who have enrolled in a previous setmelanotide trial (e.g., the open-label study to evaluate the safety and efficacy of setmelanotide in subjects with
- 15 hypothalamic obesity) and achieved therapeutic efficacy and safety criteria as determined by the Investigator.
2. Ability to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and sign the written informed consent, or, for patients aged < 18 years, a parent/legal guardian that can sign.
- 20 3. Patient must meet one of the following contraception requirements:
 - If a female of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must use a highly effective form of contraception.
 - 25 • If a female of non-childbearing potential, defined as permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or post-menopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone [FSH] level in the post-menopausal laboratory range), contraception is not required during the study.
 - 30 • Younger female patients who have not reached menarche upon study entry will be assessed for Tanner staging and at first menarche will be required to comply with

contraception requirements and pregnancy testing as outlined in the protocol.

- If a male with female partner(s) of childbearing potential, must agree to a double barrier method if they become sexually active during the study. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the study.

5 Exclusion Criteria

1. Pregnant and/or breastfeeding or desiring to become pregnant during this trial.
2. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. Any
10 concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for study participation.
3. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially
15 clinically significant disease should be reviewed with the Sponsor to determine eligibility.
4. Diagnosis of severe psychiatric disorders (e.g., schizophrenia, bipolar disorder, personality disorder or Major Depressive Disorder (MDD)).5. Any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month.
- 20 6. Current or prior diagnosis of a significant liver disease
7. Glomerular filtration rate (GFR) <30 mL/min during Screening.
8. History or close family history (parents or siblings) of skin cancer or melanoma (not including noninvasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.

25 Results for the HO Subpopulation of Patients

- 5 patients from the Phase 2 study of setmelanotide for treating subjects with hypothalamic obesity continued treatment with setmelanotide in the long-term extension study. All of the patients achieved significant reductions in BMI during the initial Phase 2 study, and all of the patients but one continued to further see reductions in BMI for an additional 3-8 months. The
30 fifth patient who experienced an increase in BMI in the long-term extension study period, however, did not return to his or her original BMI at the initiation of the Phase 2 study.

Example 3: A study to evaluate the safety and efficacy of setmelanotide in subjects with hypothalamic obesity

Purpose

5 This example describes a phase 3 study that seeks to evaluate the change in body mass index in response to setmelanotide administered subcutaneously (SC) daily in patients with hypothalamic obesity (HO). Additional objectives of this study include evaluation of changes in parameters of body weight, body mass index (BMI), waist circumference, and quality of life in response to setmelanotide in patients with HO and to evaluate the safety and tolerability of setmelanotide in patients with HO. In addition, this study seeks to evaluate changes in weight, BMI, hunger, waist circumference, hyperphagia, hunger, and quality of life in patients that were being administered setmelanotide for a total of 12 months and in patients being administered setmelanotide for only 6 months at the end of the open label part (6 months).

15 Investigational Study Drug

Setmelanotide, 10 mg/mL in a sterile solution for injection, will be provided at 1.0, 2.0, 3.0 mg QD for patients 6 to <16 years of age, and 2.0 to 3.0 mg QD for patients ≥16 years of age.

Primary Endpoints

20 The primary endpoint of this study is to evaluate the % change in BMI in response to setmelanotide administered subcutaneously (SC) daily in patients with hypothalamic obesity (HO) compared to placebo at the end of placebo-controlled study.

Secondary Endpoints

The secondary endpoints include evaluation of:

- 25 • changes in parameters of body weight, waist circumference, and quality of life in response to setmelanotide in patients with HO at the end of the 6-month placebo-controlled study
- changes in physical activity and sleep in patients with HO compared to placebo at the end of the 6-month placebo-controlled study
- changes in parameters of body weight, waist circumference, hunger, hyperphagia and quality of life in response to setmelanotide in patients that were on setmelanotide a total of 12
- 30

months and on patients that were on setmelanotide only 6 months at the end of the open label part (12 months)

• changes in physical activity and sleep in patients that were on setmelanotide a total of 12 months and on patients that were on setmelanotide only 6 months at the end of the open label part (12 months)

• change in metabolic parameters following treatment with setmelanotide compared to placebo at the end of the 6-month placebo-controlled part.

• change in metabolic parameters following treatment with setmelanotide in patients that were on setmelanotide a total of 12 months and on patients that were on setmelanotide only 6 months at the end of the open label part (12 months).

• change in biomarkers following treatment with setmelanotide compared to placebo at the end of the 6-month placebo-controlled part
low-density lipoprotein [LDL]-cholesterol, triglycerides).

• change in biomarkers following treatment with setmelanotide in patients that were on setmelanotide a total of 12 months and on patients that were on setmelanotide only 6 months at the end of the open label part (12 months).

Study Design Rationale

This study describes a Phase 3, multicenter, placebo-controlled, randomized 2:1 (active to placebo), single registrational study, designed to assess the effect of setmelanotide on weight loss and hunger on a population affected by HO (Stage A) followed by a 6-month open label part to assess efficacy and tolerability of setmelanotide at 1 year of treatment (Stage B). Approximately 120 patients aged 4 and over are planned to be enrolled across approximately 20-25 clinical sites in the US and Europe.

Screening Period

Upon providing informed consent, patients will enter the Screening Period, during which they will be assessed for eligibility and complete all screening procedures as described in the Schedule of Activities (SoA). During the screening period patients will be asked to provide at least 3 documented data points on height for pediatric patients, and weight deriving from at least 6 months before the day of screening.

Treatment Period

Patients who are determined to be eligible, based on Screening assessments, will return to the

clinic for the Baseline Visit (Visit 2) and receive the first setmelanotide dose. The starting setmelanotide dose is dependent on patient age; however, for all patients, the setmelanotide dose will be titrated to a final dose of 3.0 mg/day (initial titration phase), as follows

Patients aged 4 and older

- 5 • Starting at Baseline (Day 1; Visit 2) through approximately Day 14, patients will receive setmelanotide 0.5 mg/day.
- Patients will be escalated every 1 week (minimum) or 2 weeks (maximum) of 0.5 mg to 1 mg depending on tolerability with the goal of reaching 3 mg by Visit 5 (week 12)
- On Visit 5 (or earlier when tolerated), patients will be started on 3 mg until week 24 (Visit 10 8).

The investigator, after conversation with the Sponsor may vary dose regimen based on tolerability and efficacy considerations.

Study Visits

- Patients will return to the study center for Visits 3, 4, 5, 6, 7, 8 (Weeks 4, 8, and 12, 16, 20, 15 24 respectively), with each of these visits conducted approximately 4 weeks apart. All patients will return to the study center at Week 24 (Visit 8) and receive the last setmelanotide or placebo injection of the placebo-controlled portion. Study endpoints are collected at Visit 8. After completion of Visit 8, participation in the current study will then proceed with 6 months open label part (Stage B).
- 20 Every patient transitioning into Stage B will follow the same escalation scheme of Stage A regardless of the treatment assignment. Patients and site staff will remain blinded to treatment assignment throughout the study.

Inclusion Criteria

Patients must meet the following criteria to be eligible for study participation:

- 25 1. Patient has documented evidence of HO so defined:
- a) Evidence of hypothalamic injury on magnetic resonance imaging (MRI); AND
- b) Diagnosis of craniopharyngioma or other non-malignant brain tumor affecting the hypothalamic region;
- c) Has undergone surgery, or chemotherapy, or radiation ≥ 6 months before Screening.
- 30 d) the investigator has acknowledged weight gain associated with the hypothalamic injury for 1 year before surgery or chemotherapy or radiotherapy and/or 6 months afterwards

2. Aged 4 and over at time of enrollment.
3. Obesity, documented by a BMI ≥ 30 kg/m² for patients ≥ 18 years of age or BMI ≥ 93 rd percentile for age and gender for patients 6 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.
- 5 4. Patients or caregivers reporting temporally related increase in hunger and/ or hyperphagia to tumor diagnosis or treatment for it and still present at screening.
5. Patient must meet one of the following contraception requirements:
 - If a female of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy,
10 bilateral salpingectomy, or bilateral oophorectomy), must use a highly effective form of contraception and for 90 days after the study as outlined in Section **Error! Reference source not found.**
 - If a female of non-childbearing potential, defined as permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or post-
15 menopausal for at least 2 months (and confirmed with a screening follicle-stimulating hormone [FSH] level in the post-menopausal laboratory range), contraception is not required during the study.
 - Younger female patients who have not reached menarche upon study entry will be assessed for Tanner staging and at first menarche will be required to comply with
20 contraception requirements and pregnancy testing as outlined in the protocol.
 - If a male with female partner(s) of childbearing potential, must agree to a double barrier method if they become sexually active during the study. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the study.
- 25 6. Ability to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and sign the written informed consent, or, for patients aged <18 years, a parent/legal guardian that can sign.
7. If receiving hormone replacement therapy (i.e., thyroid hormones, glucocorticoids, growth hormone or other medications known to affect metabolism or weight/body
30 composition), the dose of such therapy has remained stable for at least 2 months prior

to Screening. (Changes in dose of $\leq 15\%$ may be permissible, with the Sponsor's approval.)

Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study participation:

- 5 1. Weight loss $\geq 2\%$ in the previous 3 months for patients ≥ 18 years of age or $> 2\%$ reduction in BMI for pediatric patients aged 4 to < 18 years of age.
Note: Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.)
 10 are allowed if:
 - the regimen and/or dose has been stable for at least 3 months prior to randomization
 - the patient has not experienced weight loss $\geq 2\%$ during the previous 3 months, and
 - the patient intends to keep the regimen and/or dose stable throughout the course of the study.
- 15 2. Bariatric surgery or procedure (e.g., gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc.) within the last 6 months. All patients with a history of bariatric surgery or procedures must be discussed with and receive approval from the Sponsor prior to enrollment.
- 20 3. Diagnosis of severe psychiatric disorders (e.g., schizophrenia, bipolar disorder, personality disorder), or Major Depressive Disorder (MDD) within the previous 2 years, or Screening Patient Health Questionnaire (PHQ) 9/PHQ A score ≥ 15 , or any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C SSRS) during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month..
4. Glycated hemoglobin (HbA1c) $> 10.0\%$ at Screening.
- 25 5. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
6. Glomerular filtration rate (GFR) < 30 mL/min/1.73 m² during Screening.
7. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions
 30 (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. Any

concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for study participation.

8. History or close family history (parents or siblings) of skin cancer or melanoma (not including noninvasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
9. Participation in any clinical study with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first setmelanotide dose.
10. Previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
11. Inability to comply with once daily (QD) injection regimen.
12. Pregnant and/or breastfeeding or desiring to become pregnant during this trial.
13. Cognitive impairment that, in the Investigator's opinion, precludes participation to the study and completions of study procedures or questionnaires.
14. Patient is, in Investigator's opinion, otherwise not suitable to participate in the study.
15. Patients having obesity with other genetic or syndromic etiology (e.g., PPL[POMC, PCSK1, LEPR], Bardet-Biedel syndrome, Alstrom syndrome etc.) unrelated to hypothalamic trauma.
16. Previous diagnosis of Prader-Willi syndrome, rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome (ROHHADNET)
17. If the patient is undergoing hormone replacement therapy, the dose has remained unchanged for at least 2 months before entry into the Screening Period.

Duration of Treatment

All patients will receive study treatment for up to 12 months. Total study participation will last between 22 and 28 weeks, based on the variable length of the Screening Period

Treatment

All patients will receive study treatment for up to 6 months during the placebo-controlled period. Total study participation in Stage A will last between 26 to 32 weeks, based on the variable length of the Screening Period. The Open label part will last another 24 weeks.

Criteria for evaluation

Primary endpoints:

- % change in BMI from baseline after 24 weeks of setmelanotide compared to placebo.

Key Secondary Endpoint:

- Change in hunger in response to 24 weeks of setmelanotide treatment as measured by change from baseline in daily and global hunger scores in patients treated with setmelanotide compared to placebo after 24 weeks of treatment (End of Stage A).

Secondary Endpoints:

- Proportion of patients with $\geq 5\%$ reduction from baseline in BMI in adult patients (≥ 18 yo) or a reduction in BMI Z-Score of ≥ 0.2 in pediatric patients (< 18 yo) after 24 weeks of setmelanotide treatment compared to placebo
- Proportion of patients aged ≥ 4 to < 18 years with ≥ 0.2 reduction of BMI Z-score from baseline after 24 weeks of setmelanotide
- Proportion of patients with $\geq 10\%$ reduction from baseline in BMI in all patients and in patient > 18 yo after 24 weeks of setmelanotide treatment compared to placebo
- Proportion of patients with $\geq 15\%$ reduction from baseline in BMI in all patients and in patient > 18 yo after 24 weeks of setmelanotide treatment compared to placebo
- Proportion of patients achieving BMI 27 (in adults) or $< 95^{\text{th}}$ (in peds) after 24 weeks on setmelanotide
- Average BMI z and BMI percentile reduction in patients < 18 yo after 24-weeks on setmelanotide
- Mean percent Change from baseline in weight in patients ≥ 18 years after 60 weeks of setmelanotide treatment compared to placebo.
- Average change in hyperphagia symptoms total score from Baseline to Week 24
- Average change in the weekly average of the daily most hunger score in patients capable of completing the questionnaire (patients ≥ 12 yo)
- The proportion of patients ≥ 12 years old, who achieve a ≥ 2 point reduction (improvement) from Baseline to end of Week 60 ~~Stage A (Week 24)~~ in the weekly average of the daily maximal hunger score for the setmelanotide group compared to the placebo group. Mean percent change in the weekly average of the daily maximal hunger score from Baseline to end of Stage A (Week 24) in patients ≥ 12 years old on setmelanotide treatment compared to placebo

- Mean change from Baseline to end of Stage A (Week 24) in physical functioning score and total score for the Impact of Weight on Quality of Life-Lite (IWQOL) (IWQOL-Lite in patients ≥ 18 years old and IWQOL-Kids in patients 11- <18 years old), on setmelanotide treatment compared to placebo
- 5 • Safety and tolerability of setmelanotide injection as determined by the presentation, frequency, and severity of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)

Other Secondary Endpoints:

- 10 • Change from baseline in waist circumference in patients aged ≥ 18 years after 24 weeks of setmelanotide treatment compared to placebo
- Mean change from Baseline to end of Stage A (Week 24) in total score for the 5-level EuroQol 5 Dimension questionnaire (EQ-5D-5L in patients ≥ 16 years old and EQ-5D-5L Proxy version in patients <16 years old) on setmelanotide treatment compared to placebo
- 15 • Mean change from Baseline to ~~Week 60~~~~end of Stage A (Week 24)~~ in physical functioning score and total score for the Impact of Weight on Quality of Life-Lite (IWQOL) (IWQOL-Lite in patients ≥ 18 years old and IWQOL-Kids in patients 11- <18 years old), on setmelanotide treatment compared to placebo
- Mean change from Baseline to end of Stage A (Week 24) in steps measured by actigraphy in patients on setmelanotide treatment compared to placebo,
- 20 • Mean change from Baseline to end of Stage A (Week 24) in sleep hours measured by actigraphy in patients on setmelanotide treatment compared to placebo,

Exploratory Endpoints:

- 25 • Change from baseline in metabolic parameters following treatment with setmelanotide, including fasting glucose, HbA1c, lipid profiles (total-, high-density lipoprotein [HDL]-, and low-density lipoprotein [LDL]-cholesterol, triglycerides) compared to placebo at the end of the 24 weeks (end of stage A)
- Change from baseline in metabolic parameters following treatment with setmelanotide, including fasting glucose, HbA1c, lipid profiles (total-, high-density lipoprotein [HDL]-, and low-density lipoprotein [LDL]-cholesterol, triglycerides)
- 30 compared to placebo at the end of the Stage B months

- Proportion of patients with $\geq 5\%$ reduction from baseline in BMI in all patients and in patient >18 yo at the end of Stage B comparing pts on set for 24 weeks vs 48 weeks
- Proportion of patients aged ≥ 6 to <18 years with ≥ 0.2 reduction of BMI Z-score from baseline the end of Stage B comparing pts on set for 24 weeks vs 48 weeks
- 5 • Proportion of patients with $\geq 10\%$ reduction from baseline in BMI in all patients and in patient >18 yo at the end of Stage B comparing pts on set for 24 weeks vs 48 weeks
- Proportion of patients with $\geq 15\%$ reduction from baseline in BMI in all patients and in patient >18 yo the end of Stage B comparing pts on set for 24 weeks vs 48 weeks
- 10 • Proportion of patients achieving BMI <27 (in adults) or $<95^{\text{th}}$ (in peds) the end of Stage B comparing pts on set for 24 weeks vs 48 weeks
- Average BMI zZ-Score and BMI percentile reduction in patients <18 yo at the end of Stage B comparing pts on set for 24 weeks vs 48 weeks a
- Mean percent Change from baseline in weight in patients > 18 years the end of Stage
- 15 B comparing pts on set for 24 weeks vs 48 weeks

Safety Endpoints:

Safety and tolerability assessed by the frequency and severity of AEs, vital signs, and laboratory evaluations at the end Stage A in all patients treated with setmelanotide compared to placebo.

20

EQUIVALENTS

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has
 25 been disclosed with reference to specific aspects, it is apparent that other aspects and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such aspects and equivalent variations.

CLAIMS

1. A method of treating hypothalamic obesity in a subject comprising administering to the subject a melanocortin-4 receptor (MC4R) agonist, wherein the subject:
 - (i) has or is identified as having hypothalamic obesity;
 - (ii) has or is identifying as having damage to the brain tissue;
 - (iii) has or is identified as having a proliferative brain disease,thereby treating hypothalamic obesity in the subject.
2. The method of claim 1, comprising (i).
3. The method of claim 1, comprising (ii).
4. The method of claim 1, comprising (iii).
5. The method of claim 1, wherein the hypothalamic obesity is caused by a neurodevelopmental abnormality or a brain malformation.
6. The method of claim 1, wherein the damage to the brain tissue is present in the hypothalamus.
7. The method of claim 6, wherein the damage to the brain tissue is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or arcuate hypothalamic nucleus.
8. The method of claim 7, wherein the damage or trauma in the brain occurs in the ventromedial nucleus.
9. The method of claim 1, wherein the subject has hypothalamic obesity.

10. The method of claim 1, wherein the proliferative brain disease comprises a benign tumor, a benign lesion, or a malignant tumor (e.g., cancer).

11. The method of claim 10, wherein the proliferative brain disease is present in the hypothalamus.

12. The method of claim 10, wherein the proliferative brain disease is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or arcuate hypothalamic nucleus.

13. The method of claim 10, wherein the proliferative brain disease comprises craniopharyngioma or astrocytoma.

14. The method of claim 1, wherein the subject has undergone a surgery (e.g., tumor removal or bariatric surgery) or received radiation.

15. The method of claim 1, wherein the subject is obese, e.g., severely obese.

16. The method of claim 1, wherein the subject is hyperphagic.

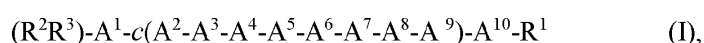
17. The method of claim 1, wherein the subject has a body mass index (BMI) greater than 35 kg/m² (e.g., $\geq 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50$ kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

18. The method of claim 1, wherein the subject has a body mass index (BMI) greater than 40 kg/m² (e.g., $\geq 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55$ kg/m² or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

19. The method of claim 1, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

5 20. The method of claim 1, wherein the subject has a lower body weight after administration of the MC4R agonist than before administration of the MC4R agonist.

21. The method of claim 1, wherein the MC4R agonist is has the structure of Formula (I):



10 wherein:

A^1 is Acc, $HN-(CH_2)_m-C(O)$, L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β -Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or $(X^1, X^2, X^3, X^4, X^5)Phe$;

15 A^5 is D-Phe, Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D- $(X^1, X^2, X^3, X^4, X^5)Phe$, or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or $HN-CH((CH_2)_n-N(R^4R^5))-C(O)$;

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, $HN-(CH_2)_s-C(O)$,

20 or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, $HN-(CH_2)_r-C(O)$, L- or D-amino acid, or deleted;

R^1 is OH or NH_2 ;

25 each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, $(C_1-C_{30})alkyl$, $(C_1-C_{30})heteroalkyl$, $(C_1-C_{30})acyl$, $(C_2-C_{30})alkenyl$, $(C_2-C_{30})alkynyl$, $aryl(C_1-C_{30})alkyl$, $aryl(C_1-C_{30})acyl$, substituted $(C_1-C_{30})alkyl$, substituted $(C_1-C_{30})heteroalkyl$, substituted $(C_1-C_{30})acyl$, substituted $(C_2-C_{30})alkenyl$, substituted $(C_2-C_{30})alkynyl$, substituted $aryl(C_1-C_{30})alkyl$, and substituted $aryl(C_1-C_{30})acyl$;

30 each of R^4 and R^5 is, independently for each occurrence, H, $(C_1-C_{40})alkyl$, $(C_1-C_{40})heteroalkyl$, $(C_1-C_{40})acyl$, $(C_2-C_{40})alkenyl$, $(C_2-C_{40})alkynyl$, $aryl(C_1-C_{40})alkyl$,

aryl(C₁-C₄₀)acyl, substituted (C₁-C₄₀)alkyl, substituted (C₁-C₄₀)heteroalkyl, substituted (C₁-C₄₀)acyl, substituted (C₂-C₄₀)alkenyl, substituted (C₂-C₄₀)alkynyl, substituted aryl(C₁-C₄₀)alkyl, substituted aryl(C₁-C₄₀)acyl, (C₁-C₄₀)alkylsulfonyl, or -C(NH)-NH₂;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

5 n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X¹, X², X³, X⁴, and X⁵ each is, independently for each occurrence, H, F, Cl, Br, I, (C₁-C₁₀)alkyl, substituted (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, substituted (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, substituted (C₂-C₁₀)alkynyl, aryl, substituted aryl, OH, NH₂, NO₂, or CN.

10

22. The method of claim 21, wherein A¹ is selected from Lys, D-Lys, Arg, and D-Arg.

23. The method of claim 21, wherein A² and A⁹ are each independently selected from Cys, hCys, and Pen.

15

24. The method of claim 21, wherein A³ is selected from Ala or D-Ala.

25. The method of claim 21, wherein A⁴ is selected from His and D-His.

20

26. The method of claim 21, wherein A⁵ is selected from Phe, D-Phe, D-1-Nal, and D-2-Nal.

27. The method of claim 21, wherein A⁶ is Arg.

25

28. The method of claim 21, wherein A⁷ is Trp.

29. The method of claim 21, wherein A⁸ and/or A¹⁰ is deleted.

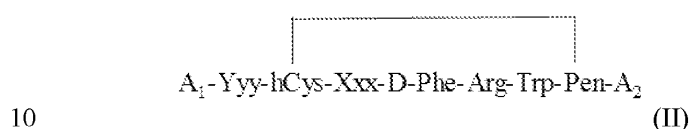
30. The method of claim 21, wherein R¹ is NH₂.

30

31. The method of claim 21, wherein one of R^2 and R^3 is independently hydrogen and the other of R^2 and R^3 is independently (C_1 - C_{30}) acyl (e.g., acetyl).

32. The method of claim 1, wherein the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ (SEQ ID NO: 140).

33. The method of claim 1, wherein the MC4R agonist has the structure of Formula (II) or a pharmaceutically acceptable salt thereof.



where Xxx is Asn, Gln, Ser, or Thr,

where A₁ is H or Ac,

where A₂ is OH or NH₂, and

where Yyy is Lys, Arg, D-Lys, or D-Arg.

15

34. The method of claim 33, wherein the MC4R agonist is selected from:

SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

20 (SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH₂;

(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

25 (SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

- (SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
5 (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
10 (SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
15 (SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
20 (SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
25 (SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
30 (SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

- (SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
5 (SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
10 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
15 (SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
20 (SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and
(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂,
or a pharmaceutically acceptable salt thereof.

35. The method of claim 1, wherein the MC4R agonist is formulated as a pharmaceutical
25 composition.

36. The method of claim 35, wherein the pharmaceutical composition further comprises a
pharmaceutically acceptable excipient.

37. The method of claim 35, wherein the pharmaceutical composition comprises a polyethylene glycol (e.g., a modified polyethylene glycol, e.g., mPEG-DSPE, e.g., mPEG-2,000-DSPE).

5 38. The method of claim 1, comprising administering the MC4R agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

39. The method of claim 38, wherein the unit dosage form is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe), an implantable device, a needleless
10 hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

40. The method of claim 39, wherein the MC4R agonist is administered subcutaneously, e.g., by subcutaneous injection.

15

41. The method of claim 1, wherein the subject is a human.

42. The method of claim 1, wherein the subject is an adult (e.g., over the age of 18 years old).

20

43. The method of claim 1, wherein the subject is a pediatric subject, e.g., a child (e.g., under the age of 18, 16, 14, 12, 10, 8, 6, or 4 years).

44. The method of claim 1, wherein prior to administration of the MC4R agonist, the
25 subject has previously received treatment for obesity, e.g., a non-genetic obesity, e.g., hypothalamic obesity.

45. The method of claim 1, wherein after a first administration of the MC4R agonist (e.g., at least 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 4 months, 5 months, 6
30 months, 8 months, 10 months, 1 year, or longer), the subject exhibits a reduction in BMI.

46. The method of claim 45, wherein the reduction of BMI in the subject is greater than 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, or more, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

5

47. The method of claim 45, wherein the reduction of BMI in the subject is greater than 0.5%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

10 48. The method of claim 45, wherein the reduction of BMI in the subject is greater than 5%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

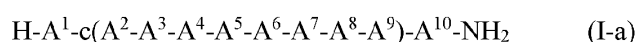
15 49. The method of claim 45, wherein the reduction of BMI in the subject is greater than 10%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

20 50. The method of claim 45, wherein the reduction of BMI in the subject is between 1%-10% (e.g., 1-5%, or 5-10%), e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

51. The method of claim 45, wherein the reduction of BMI in the subject occurs between 8 weeks and 6 months after administration of the MC4R agonist.

25 52. The method of claim 1, wherein the subject is administered an additional agent (e.g., an additional therapeutic agent).

53. The method of claim 1, wherein the MC4R agonist is a compound of Formula (I-a):



30 or a pharmaceutically acceptable salt thereof, wherein:

A¹ is Phe, D-Phe, or Nle;

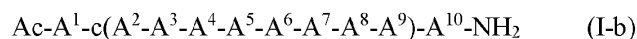
A^2 is Cys;
 A^3 is deleted;
 A^4 is His;
 A^5 is D-Phe or D-(Et)Tyr;
5 A^6 is Arg or hArg;
 A^7 is Trp or Bip;
 A^8 is Ala, β -Ala, Gaba, or Apn;
 A^9 is D-Cys; and
 A^{10} is Thr or deleted.

10

54. The method of claim 53, wherein the MC4R agonist of Formula (I-a) is selected from:

(SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp- β -Ala-D-Cys)-Thr-NH₂;
 15 (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp- β -Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp- β -Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip- β -Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp- β -Ala-D-Cys)-Thr-NH₂;
 20 (SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip- β -Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip- β -Ala-D-Cys)-Thr-NH₂;
 (SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂; and
 (SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂.

25 55. The method of claim 1, wherein the MC4R agonist is a compound of Formula (I-b):



or a pharmaceutically acceptable salt thereof, wherein:

A^1 is Nle, A6c, D-2-Nal, Cha, Oic, Chg, hCha, D-Cha, D-hCha, Nip, hPro, hLeu, Phe, D-Phe, D-Chg, hPhe, β -hMet, Gaba, Leu, Ile, Val, 2-Nal, Arg or D-Arg;

30 A^2 is Asp, Cys, D-Cys, or Pen;

- A³ is D-Ala, β -Ala, Gaba, Aib, Gly, Ala, D-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, deleted;
- A⁴ His or 3-Pal;
- A⁵ is Phe, D-Phe, or D-2-Nal;
- 5 A⁶ is Arg;
- A⁷ is Trp, 1-Nal, 2-Nal, Bal, or D-Trp;
- A⁸ is β -Ala, A6c, Ahx, Apn, Gaba, Ala, Aha, D-Ala or deleted;
- A⁹ is Lys, Cys, D-Cys, or Pen;
- A¹⁰ is deleted.
- 10 wherein A² and A⁹ are pairwise selected to form a disulfide or lactam bridge.

56. The method of claim 55, wherein the MC4R agonist of Formula (I-b) is selected from:

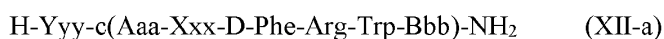
- (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp- β -Ala-Lys)-NH₂;
- 15 (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH₂;
- (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH₂;
- (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH₂;
- (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH₂;
- (SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- 20 (SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
- (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 14) Ac-Nle-c(Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- 25 (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- 30 (SEQ ID NO: 20) Ac-Nle-c(D-Cys- β -Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
- (SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH₂;

- (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
5 (SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
10 (SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH₂;
(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
15 (SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
20 (SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
25 (SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
30 (SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH₂;

- (SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH₂;
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH₂;
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH₂;
5 (SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH₂;
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH₂;
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH₂;
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH₂;
10 (SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH₂;
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH₂;
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH₂;
15 (SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH₂;
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH₂;
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH₂;
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH₂;
20 (SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH₂;
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH₂;
25 (SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH₂;
30 (SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH₂;
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;

- (SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 5 (SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH₂;
 10 (SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH₂;
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH₂;
 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH₂;
 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH₂;
 15 (SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
 (SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH₂;
 (SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 (SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂;
 20 (SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH₂;
 (SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂; and
 25 (SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH₂.

57. The method of claim 1, wherein the MC4R agonist is a compound of Formula (XII-a):



30 or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

- 5 58. The method claim 57, wherein the MC4R agonist of Formula (XII-a) is selected from:
- (SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
- 10 (SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
- 15 (SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
- (SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
- 20 (SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and
- (SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

59. The method of claim 1, wherein the MC4R agonist is a compound of Formula (XII-b):



or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

30 Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

60. The method of claim 59, wherein the MC4R agonist of Formula (XII-b) is selected from:

- (SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 5 (SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Apr)-NH₂;
 (SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 10 (SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;
 15 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 (SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
 20 (SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂; and
 (SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂.

61. The method of claim 1, wherein the MC4R agonist is a compound of Formula (XII-c):



or a pharmaceutically acceptable salt thereof, wherein:

A₁ is H or Ac;

A₂ is OH or NH₂;

Yyy is L-Arg or D-Arg;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and

Xxx is Asn, Gln, Ser, or Thr.

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62. The method of claim 61, wherein the MC4R agonist of Formula (XII-c) is selected from:

(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

10 (SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Apr)-NH₂;

(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

15 (SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

20 (SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH₂;

25 (SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

30 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH₂;

(SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
5 (SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH₂;
(SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH; and
(SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH.

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63. The method of claim 1, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI of between 5-10, e.g., after 16 weeks, relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist.

15 64. The method of claim 63, wherein the subject is a pediatric subject between ages 6 and 18.

65. The method of claim 1, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight of between about 5 kg to about 15 kg, e.g., after 16 weeks,
20 relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist.

66. The method of claim 65, wherein the subject is a pediatric subject between ages 6 and 18.

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