

NON-NATURALLY OCCURRING MELANOCORTIN ANALOGS AND USES  
THEREOF FOR MODULATING WEIGHT GAIN

CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of U.S. Provisional Patent Application No. 63/607,500, filed December 7, 2023, U.S. Provisional Patent Application No. 63/618,843, filed January 8, 2024, U.S. Provisional Patent Application No. 63/557,385, filed February 23, 2024, U.S. Provisional Patent Application No. 63/573,429, filed April 2, 2024, U.S. Provisional Patent Application No. 63/650,705, filed May 22, 2024, U.S. Provisional Patent Application No. 63/656,583, filed June 5, 2025, and U.S. Provisional Patent Application No. 63/663,648, filed June 24, 2024, all of which applications are incorporated herein by reference in their entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

**[0002]** This application contains an ST.26 compliant Sequence Listing, which is submitted concurrently in xml format and hereby incorporated by reference in its entirety. The .xml copy, created on created on December 9, 2024, is titled "146316\_8017\_WO00\_SL.xml" and is 421,967 bytes in size.

BACKGROUND

**[0003]** The prevalence of obesity, diabetes, and metabolic syndrome has reached pandemic proportions, and is expected to continue to rise in the next two decades. These conditions place enormous stress on healthcare systems globally. Accordingly, various weight loss agents have been developed in an attempt to treat such conditions. Although some weight loss agents have been approved for ongoing use, many are not sufficiently effective in achieving desired amounts or types of weight loss.

**[0004]** Accordingly, despite recent advances treatment for obesity, diabetes, and metabolic syndrome, there is a demand for novel approaches to make weight loss agents more effective.

## SUMMARY

**[0005]** In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in a subject in need thereof, including administering to the subject: (a) a GLP-1 receptor agonist; and (b) a non-naturally occurring melanocortin analog, to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject.

**[0006]** In some embodiments, the present technology comprises use of (a) a non-naturally occurring melanocortin analog and (b) a GLP-1 receptor agonist for reducing body weight and/or fat mass in a subject in need thereof to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject.

**[0007]** In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in a subject in need thereof, including administering to the subject: a non-naturally occurring melanocortin analog including a sequence of Formula (I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge



between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0008]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, the non-naturally occurring melanocortin analog including a sequence of Formula (I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0009]** In some embodiments, the present technology comprises a method or the use, wherein the method further includes reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

**[0010]** In some embodiments, the present technology comprises a method 5, wherein the lean mass is lean muscle mass.

**[0011]** In some embodiments, the present technology comprises a method or the use, wherein the method further includes treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in the subject.

**[0012]** In some embodiments, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, including administering to the subject: (a) a GLP-1 receptor agonist; and (b) a non-naturally occurring melanocortin analog, to produce a synergistic or additive effect on glucose intolerance and/or diabetes mellitus in the subject.

**[0013]** In some embodiments, the present technology comprises use of (a) a non-naturally occurring melanocortin analog and (b) a GLP-1 receptor agonist for treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof to produce a synergistic or additive effect on glucose intolerance and/or diabetes mellitus in the subject

**[0014]** In some embodiments, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, including administering to the subject: a non-naturally occurring melanocortin analog including a sequence of Formula: X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys),

proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0015]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog for treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, the non-naturally occurring melanocortin analog including a sequence of Formula (I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine

(p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0016]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

**[0017]** In some embodiments, the present technology comprises a method or the use, wherein the lean mass is lean muscle mass.

**[0018]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes reducing body weight and/or fat mass in the subject.

**[0019]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes treating, preventing, reducing, or otherwise ameliorating a sleep disorder in the subject.

**[0020]** In some embodiments, the present technology comprises a method or the use, wherein the sleep disorder is sleep apnea.

**[0021]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is administered at a dose that is less than a dose required to elicit a response in the subject without the non-naturally occurring melanocortin analog.

**[0022]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered at a dose that is less than a dose required to elicit a response in the subject without the GLP-1 receptor agonist or the dual GLP-1/GIP receptor agonist.

**[0023]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 0.01 mg to about 10 mg once per week.

**[0024]** In some embodiments, the present technology comprises a method or the use, wherein semaglutide is administered subcutaneously at a dose of less than 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week.

**[0025]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 0.5 mg to about 40 mg once daily.

**[0026]** In some embodiments, the present technology comprises a method or the use, wherein semaglutide is administered orally at a dose of less than 3 mg, 7 mg or 14 mg once daily.

**[0027]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 12.5 nmol/kg or 25 nmol/kg per body weight of the subject once every three days.

**[0028]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is exenatide and is administered at a dose of about 0.5 mg to about 100 mg twice daily.

**[0029]** In some embodiments, the present technology comprises a method or the use, wherein exenatide is administered subcutaneously at a dose of less than 5 mg or 10 mg twice daily.

**[0030]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is exenatide and is administered at a dose of about 0.5 mg to about 50 mg once per week.

**[0031]** In some embodiments, the present technology comprises a method or the use, wherein exenatide is administered subcutaneously at a dose of less than 2 mg once per week.

**[0032]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is dulaglutide and is administered at a dose of about 0.05 mg to about 50 mg once per week.

**[0033]** In some embodiments, the present technology comprises a method or the use, wherein dulaglutide is administered subcutaneously at a dose of less than 0.75 mg, 1.5 mg, 3.0 mg or 4.5 mg once per week.

**[0034]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is orforglipron and is administered at a dose of about 0.01 mg to about 100 mg once daily.

**[0035]** In some embodiments, the present technology comprises a method or the use, wherein orforglipron is administered orally at a dose of less than 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, or 24 mg once daily.

**[0036]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is a dual GLP-1/GIP receptor agonist.

**[0037]** In some embodiments, the present technology comprises a method or the use, wherein the dual GIP/GLP-1 receptor agonist is tirzepatide and is administered at a dose of about 0.5 mg to about 50 mg once per week.

**[0038]** In some embodiments, the present technology comprises a method or the use, wherein tirzepatide is administered subcutaneously at a dose of less than 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg once per week.

**[0039]** In some embodiments, the present technology comprises a method or the use, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and is administered at a dose of about 12.5 nmol/kg or 25 nmol/kg per body weight of the subject once every three days.

**[0040]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.5 mg/kg to about 10 mg/kg per body weight of the subject once daily.

**[0041]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 1 mg/kg or 3 mg/kg per body weight of the subject once daily.

**[0042]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

**[0043]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

**[0044]** In some embodiments, the present technology comprises a method or the use, wherein the melanocortin 4 receptor agonist is an agonist of the melanocortin 3 receptor.

**[0045]** In some embodiments, the present technology comprises a method or the use, wherein the melanocortin 4 receptor agonist is a full agonist of the melanocortin 3 receptor.

**[0046]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin agonist includes no melanocortin 3 receptor antagonist activity.

**[0047]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to administration of the GLP-1 receptor agonist, and wherein administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the GLP-1 receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin 4 receptor analog.

**[0048]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin agonist is administered to the subject after administration of the GLP-1 receptor agonist, and wherein the subject failed to lose sufficient body weight and/or fat mass following administration with the GLP-1 receptor agonist without the non-naturally occurring melanocortin analog.

**[0049]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered to the subject after administration of the GLP-1 receptor agonist for one dose, one week, or one cycle.

**[0050]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered to the subject after treatment with the GLP-1 receptor agonist is complete.

**[0051]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is administered to the subject for a period of time before administration of the non-naturally occurring melanocortin analog, and wherein, while the non-naturally occurring melanocortin analog is administered to the subject, administration of the GLP-1 receptor agonist is paused, and wherein, when administration of the non-naturally occurring melanocortin analog is completed, administration of the GLP-1 receptor agonist is resumed.

**[0052]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog is administered to the subject for a period of time before administration of the GLP-1 receptor agonist, and wherein, while the non-GLP-1 receptor agonist is administered to the subject, administration of the non-naturally occurring melanocortin analog is paused, and wherein, when administration of the GLP-1 receptor agonist is completed, administration of the non-naturally occurring melanocortin analog is resumed.

**[0053]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes preventing or reducing one or more side effects associated with the GLP-1 receptor agonist.



**[0054]** In some embodiments, the present technology comprises a method or the use, wherein the one or more side effects associated with the GLP-1 receptor agonist is a gastrointestinal effect.

**[0055]** In some embodiments, the present technology comprises a method or the use, wherein the gastrointestinal effect is one or more of nausea, vomiting, and diarrhea.

**[0056]** In some embodiments, the present technology comprises a method or the use, wherein the one or more side effects associated with the GLP-1 receptor agonist is an adverse cardiovascular event.

**[0057]** In some embodiments, the present technology comprises a method or the use, wherein the adverse cardiovascular event is one or more of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, and peripheral vascular disease.

**[0058]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes preventing or reducing one or more side effects associated with the non-naturally occurring melanocortin analog.

**[0059]** In some embodiments, the present technology comprises a method or the use, wherein the one or more side effects associated with the non-naturally occurring melanocortin analog is an adverse cardiovascular event.

**[0060]** In some embodiments, the present technology comprises a method or the use, wherein the adverse cardiovascular event is sinus tachycardia.

**[0061]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes reducing obesity-related inflammation in the subject.

**[0062]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes preserving or improving kidney function in the subject.

**[0063]** In some embodiments, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with the use of a GLP-1 receptor agonist in a subject, including administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the GLP-1 receptor agonist.

**[0064]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin receptor agonist for treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with the use of a GLP-1 receptor agonist in a subject, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to, during, and/or after administration of the GLP-1 receptor agonist.

**[0065]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor is administered at a dose sufficient to elicit weight loss in the subject, and wherein the dose sufficient to elicit weight loss in the subject is lower than a dose of the GLP-1 receptor agonist required to elicit weight loss in the subject without the non-naturally occurring melanocortin analog.

**[0066]** In some embodiments, the present technology comprises a method or the use, wherein the one or more side effects associated with the use of a GLP-1 receptor agonist is an adverse cardiovascular event.

**[0067]** In some embodiments, the present technology comprises a method or the use, wherein the adverse cardiovascular event is one or more of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, and peripheral vascular disease.

**[0068]** In some embodiments, the present technology comprises a method or the use, wherein the one or more side effects associated with the use of the GLP-1 receptor agonist is a gastrointestinal effect.

**[0069]** In some embodiments, the present technology comprises a method or the use, wherein the gastrointestinal effect is one or more of nausea, vomiting, and diarrhea.

**[0070]** In some embodiments, the present technology comprises a method of reducing obesity-related inflammation in a subject in need thereof, including administering to the subject: (a) a GLP-1 receptor agonist; and (b) a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist

**[0071]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for reducing obesity-related inflammation in a subject in need thereof, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

**[0072]** In some embodiments, the present technology comprises a method of reducing obesity-related inflammation in a subject in need thereof, including administering to the subject a non-naturally occurring melanocortin analog including a sequence of Formula (I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or

R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0073]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog for reducing obesity-related inflammation in a subject in need thereof, wherein the non-naturally occurring melanocortin analog includes a sequence of Formula (I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3

are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0074]** In some embodiments, the present technology comprises a method of preserving or improving kidney function in a subject in need thereof, including administering to the subject: (a) a GLP-1 receptor agonist; and (b) a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

**[0075]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for preserving or improving kidney function in a subject in need thereof, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

**[0076]** In some embodiments, the present technology comprises a method of preserving or improving kidney function in a subject in need thereof, including administering to the subject: a non-naturally occurring melanocortin analog including a sequence of Formula (I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal,

dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0077]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog for preserving or improving kidney function in a subject in need thereof, wherein the non-naturally occurring melanocortin analog includes a sequence of Formula (I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNa(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and

R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0078]** In some embodiments, the present technology comprises a method or the use, wherein the subject has a metabolic dysfunction selected from the group consisting of obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies.

**[0079]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use increases tolerance for the GLP-1 receptor agonist relative to a treatment including administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[0080]** In some embodiments, the present technology comprises a method or the use, wherein the increased tolerance includes reduced nausea.

**[0081]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use maintains or increases a muscle mass level relative to a treatment including administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[0082]** In some embodiments, the present technology comprises a method or the use, wherein the muscle mass includes lean muscle mass.

**[0083]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use increases a preference level or a compliance level for the GLP-1 receptor agonist relative to a treatment including administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[0084]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use includes increasing a weight loss level for the GLP-1 receptor agonist relative to a treatment including administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[0085]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use includes a reduction in one or more side effects associated with the GLP-1 receptor agonist relative to a treatment including administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[0086]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use includes reducing a weight loss plateau for the GLP-1 receptor agonist relative to a treatment including administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[0087]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use reduces an appetite level or a weight gain level relative to a treatment including administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[0088]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use does not reduce efficacy of the GLP-1 receptor agonist relative to a control.

**[0089]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use increases efficacy of the GLP-1 receptor agonist relative to a control.

**[0090]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use does not plateau body weight loss in the subject.

**[0091]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use does not plateau fat mass loss in the subject.



**[0092]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use prevents fat mass gain after administration of the GLP-1 receptor agonist relative to a control.

**[0093]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use prevents body weight gain after administration of the GLP-1 receptor agonist relative to a control.

**[0094]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use reduces body weight gain after administration of the GLP-1 receptor agonist relative to a control.

**[0095]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use reduces fat mass gain after administration of the GLP-1 receptor agonist relative to a control.

**[0096]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use reduces a blood sugar level in the subject relative to a control.

**[0097]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use prevents a blood sugar elevation in the subject after administration of the GLP-1 receptor agonist relative to a control.

**[0098]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use reduces a blood sugar elevation in the subject after administration of the GLP-1 receptor agonist relative to a control.

**[0099]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use maintains or increases brain mass in the subject during or after administration of the GLP-1 receptor agonist relative to a control.

**[0100]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use prevents or reduces brain mass loss in the subject during or after administration of the GLP-1 receptor agonist relative to a control.

**[0101]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence of Formula

(I): X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that: when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9; when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and when R2 is Ala, then X1 is Nle.

**[0102]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (I), wherein: X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe); R3 is selected from the group

consisting of His, dHis, Pro, Phe, and glutamine (Gln); R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')); R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys); R8 is absent, Lys, or Trp; R9 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys; provided that the non-naturally occurring melanocortin analog does not include a sequence selected from the group consisting of: Ac-Nle-c[Asp-Phe-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 366); Ac-Nle-c[Asp-Phe-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 412); Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 423); Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 424); Ac-Nle-c[Asp-Phe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 487); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218); Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 225); Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231); Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291); Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300); Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302); His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 306); dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 309); Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 311); Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 312); Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 313); Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 314); Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-

NH<sub>2</sub> (SEQ ID NO: 315); Ac-Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 413); Ac-Nle-c[Asp-dHis-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 416); Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 425); Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430); Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435); Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436); Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 437); Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 438); Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 439); Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 440); Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 441); Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442); Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 443); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 447); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449); Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450); Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451); Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452); Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453); Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 454); Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 455); Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 456); Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 457); Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 458); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620); Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593); Ac-Nle-

c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 597); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 598); Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638); Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640); Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641); Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 642); Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 643); Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 644); Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 645); Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 646); Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); and Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[0103]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (IA): X<sub>1</sub>-R<sub>1</sub>-R<sub>2</sub>-R<sub>3</sub>-R<sub>4</sub>-R<sub>5</sub>-R<sub>6</sub>-R<sub>7</sub>-R<sub>8</sub>-Y<sub>1</sub>-Y<sub>2</sub>-Y<sub>3</sub>-Y<sub>4</sub> (IA), wherein: X<sub>1</sub> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R<sub>1</sub> is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R<sub>2</sub> is selected from the group consisting of Asp, Ala, and D-alanine (dAla); R<sub>3</sub> is His or dHis; R<sub>4</sub> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe); R<sub>5</sub> is His or Arg; R<sub>6</sub> is tryptophan (Trp); R<sub>7</sub> is Pro or lysine (Lys); R<sub>8</sub> is absent or lysine (Lys); Y<sub>1</sub> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y<sub>2</sub> is dVal or dPro; Y<sub>3</sub> is absent, dVal, or dPro; Y<sub>4</sub> is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sub>1</sub> or R<sub>2</sub> and R<sub>7</sub> or R<sub>8</sub> when R<sub>1</sub> or R<sub>2</sub> is Asp and R<sub>7</sub> or R<sub>8</sub> is Lys; provided that when R<sub>2</sub> is Ala, then X<sub>1</sub> is Nle.

**[0104]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (IA), wherein: X<sub>1</sub> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg); R<sub>1</sub> is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, Ala, and D-alanine (dAla); R3 is His or dHis; R4 is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe); R5 is His or Arg; R6 is tryptophan (Trp); R7 is Pro or lysine (Lys); R8 is absent or lysine (Lys); Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is dVal or dPro; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp and R7 or R8 is Lys; provided that the non-naturally occurring melanocortin analog does not include the sequence: Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[0105]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (IB): X1-R1-R2-His-R4-R5-R6-R7-R8-Y1-Y2-Y3-Y4 (IB), wherein: X1 is absent or is norleucine (Nle); R1 is selected from the group consisting of Nle, Arg, dArg, alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is Asp; R4 is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe); R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2')); R7 is Pro or Lys; R8 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R2 and R7 or R8 when R2 is Asp, and R7 or R8 is Lys.

**[0106]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (IB), wherein: X1 is absent or is norleucine (Nle); R1 is selected from the group consisting of Nle, Arg, lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis); R2 is Asp; R4 is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe); R5 is His or Arg; R6 is tryptophan (Trp); R7 is Pro or Lys; R8 is absent or Lys; Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is

dVal or dPro; Y3 is absent, dVal, or dPro; Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R2 and R7 or R8 when R2 is Asp, and R7 or R8 is Lys.

**[0107]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (IC): X1-R1-R2-His-R4-R5-R6-R7-Y1-Y2 (IC), wherein: X1 is norleucine (Nle), arginine (Arg) or D-arginine (dArg); R1 is aspartic acid (Asp); R2 is alanine (Ala) or D-alanine (dAla); R4 is D-phenylalanine (dPhe); R5 is Arg; R6 is tryptophan (Trp); R7 is Lys; Y1 is D-valine (dVal); Y2 is D-proline (dPro); and the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R2 and Lys at R7; provided that when R2 is Ala, then X1 is Nle.

**[0108]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (IC), wherein: X1 is norleucine (Nle), arginine (Arg) or D-arginine (dArg); R1 is aspartic acid (Asp); R2 is alanine (Ala) or D-alanine (dAla); R4 is D-phenylalanine (dPhe); R5 is Arg; R6 is tryptophan (Trp); R7 is Lys; Y1 is D-valine (dVal); Y2 is D-proline (dPro); and the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R2 and Lys at R7; provided that the non-naturally occurring melanocortin analog does not include a sequence of: Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[0109]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (ID): X1-R1-R2-R3-R4-R5-R6-R7-Y1-Y2-Y3 (ID), wherein: X1 is absent or is norleucine (Nle); R1 is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala); R2 is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro); R3 is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro); R4 is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of Arg, cis-4-guanidiny-

proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2')); R7 is cysteine (Cys) or lysine (Lys); Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; and a lactam bridge between R1 or R2 and R7 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 is Lys; provided that: when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present, or (ii) X1 and Y3 are absent, R1 is Nle, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; when R4 is dPhe, then (i) R3 is not His or Gln or (ii) R3 is His and either R2 is Pro or R5 is transPro(guan) or cisPro(guan); and when R4 is p(F)dPhe, R3 is His, and R1 is Nle, then (i) R6 is not Trp or (ii) Y3 is dVal.

**[0110]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes a sequence according to Formula (ID), wherein: X1 is absent or is norleucine (Nle); R1 is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala); R2 is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro); R3 is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro); R4 is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe); R5 is selected from the group consisting of Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan)); R6 is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2')); R7 is cysteine (Cys) or lysine (Lys); Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle); Y2 is selected from the group consisting of dVal, dPro, and dTle; Y3 is absent, dVal, or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; and a lactam bridge between R1 or R2 and R7 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 is Lys; provided that the non-naturally occurring melanocortin analog does not include a sequence selected from the group consisting of: Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218); Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO:



225); Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231); Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291); Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300); Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302); Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430); Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435); Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436); Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448); Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449); Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450); Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451); Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452); Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620); Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594); Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638); Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640); Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641); Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363); Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370); Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621); Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223); Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469); Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475); Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-

dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478).

**[0111]** In some embodiments, the present technology comprises a method or the use, wherein an N-terminus of the non-naturally occurring melanocortin analog, if present, is modified by an acyl group.

**[0112]** In some embodiments, the present technology comprises a method or the use, wherein the acyl group is an acetyl group.

**[0113]** In some embodiments, the present technology comprises a method or the use, wherein an N-terminus of the non-naturally occurring melanocortin analog, if present, is not modified.

**[0114]** In some embodiments, the present technology comprises a method or the use, wherein a C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group.

**[0115]** In some embodiments, the present technology comprises a method or the use, wherein a C-terminus of the non-naturally occurring melanocortin analog is not modified.

**[0116]** In some embodiments, the present technology comprises a method or the use, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond.

**[0117]** In some embodiments, the present technology comprises a method or the use, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R<sub>2</sub> and R<sub>7</sub>.

**[0118]** In some embodiments, the present technology comprises a method or the use, wherein R<sub>4</sub> is dPhe or p(F)dPhe.

**[0119]** In some embodiments, the present technology comprises a method or the use, wherein R<sub>3</sub> is His.

**[0120]** In some embodiments, the present technology comprises a method or the use, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223); Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 476); Ac-Nle-c[Asp-His-

dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363); and Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0121]** In some embodiments, the present technology comprises a method or the use, wherein R4 is p(F)dPhe.

**[0122]** In some embodiments, the present technology comprises a method or the use, wherein R1 is selected from the group consisting of Ala, Arg, dArg, Lys, dLys, His, and dHis.

**[0123]** In some embodiments, the present technology comprises a method or the use, wherein Y1 is dVal and Y2 is dPro.

**[0124]** In some embodiments, the present technology comprises a method or the use and 117-119, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 462); Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 463); Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 464); Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 465); Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 466); Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 467); and Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 468), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0125]** In some embodiments, the present technology comprises a method or the use, wherein Y1 is dTle and Y2 is dPro.

**[0126]** In some embodiments, the present technology comprises a method or the use, 117, 118, and 121, wherein the sequence according of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 479); Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 480); Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 481); Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 482); Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 483); Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 484); and Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-

Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 485), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0127]** In some embodiments, the present technology comprises a method or the use, wherein R4 is p(F)dPhe.

**[0128]** In some embodiments, the present technology comprises a method or the use, wherein at least one of X1, Y3, and Y4 is present.

**[0129]** In some embodiments, the present technology comprises a method or the use, 124, and 123, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469); Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 473); Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 474); Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475); Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0130]** In some embodiments, the present technology comprises a method or the use, wherein R5 is selected from the group consisting of His, transPro(guan) and cisPro(gaun).

**[0131]** In some embodiments, the present technology comprises a method or the use and 126, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Nle-c[Asp-His-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 228); Ac-Nle-c[Asp-His-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 229); and Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 470), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0132]** In some embodiments, the present technology comprises a method or the use, wherein R6 is dNal(2').

**[0133]** In some embodiments, the present technology comprises a method or the use and 128, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 471), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0134]** In some embodiments, the present technology comprises a method or the use, wherein R3 is not His.

**[0135]** In some embodiments, the present technology comprises a method or the use and 130, wherein R3 is selected from the group consisting of dHis, Gln, and Pro.

**[0136]** In some embodiments, the present technology comprises a method or the use, 130, and 131, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 365); Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370); Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 486); Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 491); and Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 639), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0137]** In some embodiments, the present technology comprises a method or the use, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R1 and R7 or R2 and R8.

**[0138]** In some embodiments, the present technology comprises a method or the use and 133, wherein R4 is dPhe.

**[0139]** In some embodiments, the present technology comprises a method or the use, 133, and 134, wherein R3 is His.

**[0140]** In some embodiments, the present technology comprises a method or the use and 133-135, wherein X1 and R1 are present.

**[0141]** In some embodiments, the present technology comprises a method or the use and 133-136, wherein R2 is Ala or dAla.

**[0142]** In some embodiments, the present technology comprises a method or the use and 133-137, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 268); Ac-Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 378); Ac-dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 379); and Ac-Nle-

c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 380), wherein c represents cyclization through R1 and R7 via a lactam bond.

**[0143]** In some embodiments, the present technology comprises a method or the use and 133-135, wherein either R2 or R7 is Pro.

**[0144]** In some embodiments, the present technology comprises a method or the use, 133-135, and 139, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of: Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 297); or Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 418). wherein c represents cyclization through R2 and R7 via a lactam bond.

**[0145]** In some embodiments, the present technology comprises a method or the use, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R1 and R9.

**[0146]** In some embodiments, the present technology comprises a method or the use and 141, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 420), wherein c represents cyclization through R1 and R9 via a lactam bond.

**[0147]** In some embodiments, the present technology comprises a method or the use, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a disulfide bond.

**[0148]** In some embodiments, the present technology comprises a method or the use and 142, wherein R4 is p(Cl)dPhe.

**[0149]** In some embodiments, the present technology comprises a method or the use, 142, and 143, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 498), wherein c represents cyclization through R2 and R7 via a disulfide bond.

**[0150]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498.

**[0151]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486.

**[0152]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621.

**[0153]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621.

**[0154]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 268 and 378-380.

**[0155]** In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0156]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is present in a first pharmaceutical composition.

**[0157]** In some embodiments, the present technology comprises a method or the use, wherein the first pharmaceutical composition includes one or more pharmaceutically acceptable excipients and/or carriers.

**[0158]** In some embodiments, the present technology comprises a method or the use, wherein the one or more pharmaceutically acceptable excipients and/or carriers of the first pharmaceutical composition include water.

**[0159]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0160]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is semaglutide and is present in the first pharmaceutical composition in a concentration of 0.5 mg/mL to 5.0 mg/mL, 0.5 mg/mL to 4.0 mg/mL, 0.6 mg/mL to 3.5 mg/mL, 0.65 mg/mL to 3.2 mg/mL, 0.65 mg/mL to 3.0 mg/mL, 0.8 mg/mL to 2.8 mg/mL, 1.0 mg/mL to 3.0 mg/mL, 1.0 mg/mL to 2.8 mg/mL, 1.2 mg/mL to 3.0 mg/mL, 1.2 mg/mL to 2.8 mg/mL, 0.6 mg/mL to 2.3 mg/mL, 0.6 mg/mL to 2.0 mg/mL, 0.6 mg/mL to 1.8 mg/mL, 0.6 mg/mL to 1.5 mg/mL, or 1.3 mg/mL to 2.8 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0161]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is semaglutide and is present in the first pharmaceutical composition in an amount of 0.5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg.

**[0162]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is exenatide, and is present in the first pharmaceutical composition in a concentration of 5 mg/mL to 1000 mg/mL, 10 mg/mL to 900 mg/mL, 20 mg/mL to 800 mg/mL, 50 mg/mL to 700 mg/mL, 70 mg/mL to 600 mg/mL, 90 mg/mL to 550 mg/mL, 100 mg/mL to 500 mg/mL, 110 mg/mL to 450 mg/mL, 120 mg/mL to 400 mg/mL, 130 mg/mL to 350 mg/mL, 140 mg/mL to 350 mg/mL, 150 mg/mL to 300 mg/mL, 200 mg/mL to 300 mg/mL, or 200 mg/mL to 250 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0163]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is exenatide, and is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 5.0 mg/mL, 0.25 mg/mL to 4.5 mg/mL, 0.5 mg/mL to 4.5 mg/mL, 0.75 mg/mL to 4.0 mg/mL, 1.0 mg/mL to 3.75 mg/mL, 1.25 mg/mL to 3.5 mg/mL, 1.5 mg/mL to 3.25 mg/mL, 1.75 mg/mL to 3.0 mg/mL, 2.0 mg/mL to 2.75 mg/mL, or 2.25 mg/mL to 2.5 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0164]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is dulaglutide and is present in the first pharmaceutical



composition in a concentration 0.01 mg/mL to 100 mg/mL, 0.05 mg/mL to 90 mg/mL, 0.1 mg/mL to 80 mg/mL, 0.2 mg/mL to 70 mg/mL, 0.3 mg/mL to 60 mg/mL, 0.5 mg/mL to 50 mg/mL, 0.6 mg/mL to 45 mg/mL, 0.7 mg/mL to 40 mg/mL, 0.8 mg/mL to 35 mg/mL, 0.9 mg/mL to 30 mg/mL, 1.0 mg/mL to 25 mg/mL, 1.1 mg/mL to 20 mg/mL, 1.2 mg/mL to 15 mg/mL, or 1.5 mg/mL to 10 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0165]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is orforglipron and is present in the first pharmaceutical composition in an amount of 0.01 mg to 100 mg, 0.05 mg to 90 mg, 0.1 mg to 80 mg, 0.2 mg to 70 mg, 0.3 mg to 60 mg, 0.4 mg to 50 mg, 0.5 mg to 45 mg, 0.6 mg to 40 mg, 0.7 mg to 35 mg, 0.8 mg to 30 mg, 0.9 mg to 25 mg, 1.0 mg to 20 mg, 1.1 mg to 18 mg, 1.2 mg to 16 mg, 1.3 mg to 14 mg, 1.4 mg to 12 mg, or 1.5 mg to 10 mg.

**[0166]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor is a dual GLP-1/GIP receptor agonist and is present in the first pharmaceutical composition in a concentration of 5 mg/mL to 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0167]** In some embodiments, the present technology comprises a method or the use, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and is present in the first pharmaceutical composition in a concentration of 5 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, or 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0168]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

**[0169]** In some embodiments, the present technology comprises a method or the use, wherein the first pharmaceutical composition including the GLP-1 receptor agonist is administered to the subject parenterally.

**[0170]** In some embodiments, the present technology comprises a method or the use, wherein the first pharmaceutical composition including the GLP-1 receptor agonist is administered to a subject subcutaneously.

**[0171]** In some embodiments, the present technology comprises a method or the use, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's body weight is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0172]** In some embodiments, the present technology comprises a method or the use, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's fat mass is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0173]** In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in a subject in need thereof, including: administering a GLP-1 receptor agonist to the subject for at least one treatment cycle, wherein the subject failed to lose sufficient body weight and/or fat mass following administration of the GLP-1 receptor agonist for the at least one treatment cycle; and administering a non-naturally occurring melanocortin analog including a sequence of SEQ ID NO: 295 to the subject after administration of the GLP-1 receptor agonist, such that the subject loses a sufficient amount of body weight and/or fat mass following administration of the non-naturally occurring melanocortin analog.

**[0174]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog including a sequence of SEQ ID NO: 295 for reducing body weight and/or fat mass in a subject in need thereof who has failed to lose sufficient body weight and/or fat mass following administration of a GLP-1 receptor agonist for at least one treatment cycle, wherein the non-naturally occurring melanocortin analog is administered after administration of the GLP-1 receptor agonist such that the subject loses a sufficient amount of body weight and/or fat mass.

**[0175]** In some embodiments, the present technology comprises a method of promoting weight loss in a subject currently being administered a GLP-1 receptor agonist, the method including administering to the subject a non-naturally occurring melanocortin analog, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[0176]** In some embodiments, the present technology comprises use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for reducing body weight and/or fat mass in a subject in need thereof, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[0177]** In some embodiments, the present technology comprises a method or the use, wherein the method or the use further includes treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in the subject.

**[0178]** In some embodiments, the present technology comprises a method or the use, wherein a plasma insulin level of the subject following administration of the non-naturally occurring melanocortin analog is substantially the same as a plasma insulin level of the subject prior to administration of the non-naturally occurring melanocortin analog.

**[0179]** In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in a subject in need thereof, including: administering a combination therapy including: (a) GLP-1 receptor agonist; and (b) a non-naturally occurring melanocortin analog including a sequence of SEQ ID NO: 295, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[0180]** In some embodiments, the present technology comprises use of a combination therapy including: (a) a GLP-1 receptor agonist; and (b) a non-naturally occurring melanocortin analog including a sequence of SEQ ID NO: 295, for reducing body weight and/or fat mass in a subject in need thereof, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[0181]** In some embodiments, the present technology comprises a method or the use, wherein a blood glucose level of the subject is decreased following administration of a first dose of the combination therapy.

**[0182]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is semaglutide and the combination therapy has an additive effect on the subject's weight loss.

**[0183]** In some embodiments, the present technology comprises a method or the use, wherein the combination therapy has an additive effect on the subject's fat mass loss.

**[0184]** In some embodiments, the present technology comprises the method or the use of claim 282 or 283, wherein a percent lean mass of the subject is increased following administration of a first dose of the combination therapy.

**[0185]** In some embodiments, the present technology comprises a method or the use, wherein the combination therapy has an additive effect on suppressing the subject's appetite.

**[0186]** In some embodiments, the present technology comprises a method or the use, wherein the GLP-1 receptor agonist is a dual GLP-1/GIP receptor agonist.

**[0187]** In some embodiments, the present technology comprises a method or the use, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and the combination therapy has a synergistic effect on the subject's weight loss.

**[0188]** In some embodiments, the present technology comprises a method or the use, wherein the combination therapy has a synergistic effect on the subject's fat mass loss.

**[0189]** In some embodiments, the present technology comprises a method or the use, wherein the combination therapy has a synergistic effect on the suppressing the subject's appetite.

**[0190]** In some embodiments, the present technology comprises a method or the use, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in body weight about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0191]** In some embodiments, the present technology comprises a method or the use, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, or about a 30% reduction in fat mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0192]** In some embodiments, the present technology comprises a method or the use, wherein the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0193]** In some embodiments, the present technology comprises a method or the use, wherein the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% increase in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0194]** In some embodiments, the present technology comprises a method or the use, wherein the subject exhibits about a 5%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, about a 30%, about a 35%, about a 40%, about a 45%, about a 50%, about a 60%, or about a 70% reduction, in food intake per day about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0195]** In some embodiments, the present technology comprises a method or the use, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in blood glucose level about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0196]** FIGS. 1A-1C show the cardiac data for melanocortin agonist A07D ("E2"; SEQ ID NO: 295) up to 180 minutes after subcutaneous injection.

**[0197]** FIGS. 2A-2C show the body weight and food intake of rats administered saline, 3 mg/kg (mpk) E2, 10 mg/kg E2, or 1 mg/kg setmelanotide up to 24 hours after subcutaneous injection.

**[0198]** FIGS. 3A and 3B show the plasma insulin levels of rats pre and post injection of melanocortin antagonist B07 (SEQ ID NO: 3).

**[0199]** FIGS. 4A-4N show the change in body weight of rats administered 3 mpk (mg/kg) E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg semaglutide ("Sema"; Group 4) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Sema (Group 5) after treatment.

**[0200]** FIGS. 5A-5I show the mass distribution of rats administered 3 mpk (mg/kg) E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg Sema (Group 4) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Sema (Group 5) after seven days of treatment and up to week 5 of treatment.

**[0201]** FIGS. 6A-6E show the cumulative food consumption, daily food intake, and kaolin intake in rats administered 3 mpk (mg/kg) E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg Sema (Group 4) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Sema (Group 5).

**[0202]** FIGS. 7A-7D show the blood glucose levels as measured by an oral glucose tolerance test (OGTT) of rats administered 3 mpk (mg/kg) E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg Sema (Group 4) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Sema (Group 5) on day 0 and day 8 of treatment.

**[0203]** FIGS. 8A-8N show the change in body weight of rats administered 3 mpk E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg tirzepatide ("Tirzep"; Group 7) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Tirzep (Group 6) after treatment.

**[0204]** FIGS. 9A-9I show the mass distribution of rats administered 3 mpk E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg Tirzep (Group 7) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Tirzep (Group 6) after seven days of treatment and up to week 5 of treatment.

**[0205]** FIGS. 10A-10E show the cumulative food consumption, daily food intake, and kaolin intake in rats administered 3 mpk E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg Tirzep (Group 7) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Tirzep (Group 6).

**[0206]** FIGS. 11A-11D show the blood glucose levels of rats administered 3 mpk E2 (Group 2), saline (Group 3), 12.5/25 nmol/kg Tirzep (Group 7) and a combination of 3 mpk E2 and 12.5/25 nmol/kg Tirzep (Group 6) on day 0, day 8, and day 19 of treatment.

**[0207]** FIGS. 12A-12F show the change in body weight of rats administered 1 mpk E2 (Group 1), 3 mpk E2 (Group 2), and saline (Group 3) after treatment.

**[0208]** FIGS. 13A-13F show the mass distribution of rats administered 1 mpk E2 (Group 1), 3 mpk E2 (Group 2), and saline (Group 3) after seven days of treatment.

**[0209]** FIGS. 14A-14C show the cumulative food consumption and kaolin intake over 11 days of treatment of rats administered 1 mpk E2 (Group 1), 3 mpk E2 (Group 2), and saline (Group 3).

**[0210]** FIGS. 15A-15D show the blood glucose levels of rats administered 1 mpk E2 (Group 1), 3 mpk E2 (Group 2), and saline (Group 3) on days 0 through up to day 120.

**[0211]** FIGS. 16A and 16B show gastrocnemius muscle mass as a percentage of body weight (FIG. 16A) and brain mass as a percentage of body weight (FIG. 16B) in rats administered saline vehicle, sema (12.5/25 nmol/kg), A07D ("E2"; SEQ ID NO: 295) (3mpk), A07D (3mpk) + sema (12.5/25 nmol/kg), sema (12.5/25 nmol/kg) followed by saline alone at day 21, A07D (3mpk) followed by saline alone at day 21, and A07D (3mpk) + sema (12.5/25 nmol/kg) followed by A07D alone at day 21.

**[0212]** FIGS. 17A and 17B show gastrocnemius muscle mass as a percentage of body weight (FIG. 17A) and brain mass as a percentage of body weight (FIG. 17B) in rats administered saline vehicle, tirzep (12.5/25 nmol/kg), A07D ("E2"; SEQ ID NO: 295) (3mpk),

A07D (3mpk) + tirzep (12.5/25 nmol/kg), tirzep (12.5/25 nmol/kg) followed by saline alone at day 21, A07D (3mpk) followed by saline alone at day 21, and A07D (3mpk) + tirzep (12.5/25 nmol/kg) followed by A07D alone at day 21.

**[0213]** FIGS. 18A and 18B show gastrocnemius muscle mass (FIG. 18A) and brain mass (FIG. 18B) as a percentage of body weight in rats administered saline vehicle, A07D ("E2"; SEQ ID NO: 295) (3mpk), A07D (1mpk), A07D (3mpk) followed by saline alone at day 21, and A07D (1mpk) followed by saline alone at day 21.

**[0214]** FIGS. 19A-19D show perirenal fat mass (g) (FIG. 19A), perirenal fat mass as a percentage of body weight (FIG. 19B), epididymal fat mass (g) (FIG. 19C), and epididymal fat mass as a percentage of body weight (FIG. 19D) in rats administered saline vehicle, sema (12.5/25 nmol/kg), A07D ("E2"; SEQ ID NO: 295) (3mpk), A07D (3mpk) + sema (12.5/25 nmol/kg), sema (12.5/25 nmol/kg) followed by saline alone at day 21, A07D (3mpk) followed by saline alone at day 21, and A07D (3mpk) + sema (12.5/25 nmol/kg) followed by A07D alone at day 21.

**[0215]** FIGS. 20A-20D show perirenal fat mass (g) (FIG. 20A), perirenal fat mass as a percentage of body weight (FIG. 20B), epididymal fat mass (g) (FIG. 20C), and epididymal fat mass as a percentage of body weight (FIG. 20D) in rats administered saline vehicle, tirzep (12.5/25 nmol/kg), A07D ("E2"; SEQ ID NO: 295) (3mpk), A07D (3mpk) + tirzep (12.5/25 nmol/kg), tirzep (12.5/25 nmol/kg) followed by saline alone at day 21, A07D (3mpk) followed by saline alone at day 21, and A07D (3mpk) + tirzep (12.5/25 nmol/kg) followed by A07D alone at day 21.

**[0216]** FIGS. 21A and 21B show perirenal fat mass (FIG. 21A) and epididymal fat mass (FIG. 21B) as a percentage of body weight in rats administered saline vehicle, A07D ("E2"; SEQ ID NO: 295) (3mpk), A07D (1mpk), A07D (3mpk) followed by saline alone at day 21, and A07D (1mpk) followed by saline alone at day 21.

**[0217]** FIGS. 22A-22D show the plasma and cerebrospinal fluid (CSF) concentration of A07D ("E2"; SEQ ID NO: 295) in rats over time following subcutaneous administration.



**[0218]** FIGS. 23A-23C show representative images of pancreas (FIG. 23A), heart (FIG. 23B), and liver (FIG. 23C) sections of rats fed a high fat diet and subcutaneously administered saline daily for 5 weeks.

**[0219]** FIGS. 24A and 24B show representative images of pancreas (FIG. 24A) and heart (FIG. 24B) sections of rats fed a high fat diet and subcutaneously administered 3 mg/kg A07D daily for 5 weeks.

**[0220]** FIGS. 25A-25D show changes in body weight and food intake at the beginning of treatment (FIGS. 25A and 25B) relative to the 4 weeks after removal of semaglutide (sema), tirzepatide (tirz), A07D, or saline administration (FIGS. 25C and 25D).

**[0221]** FIG. 26 shows plasma concentration of A07D administered at 1mg/kg intravenously, 10 mg/kg orally, or 30 mg/kg orally to fasted male cynomolgus monkeys.

#### DETAILED DESCRIPTION

**[0222]** The present technology comprises non-naturally occurring melanocortin analogs, or a pharmaceutically acceptable salts, solvates, or stereoisomers thereof, collectively referred to herein as melanocortin analogs, for reducing weight and/or preventing weight gain in a subject in need thereof. In some embodiments the present technology comprises combination therapies (e.g., pharmaceutical combinations) having a non-naturally occurring melanocortin analog and a weight loss agent. Use of the non-naturally occurring melanocortin analogs and the combination therapies in accordance with the present technology may be useful in treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with metabolic dysfunction. For example, the methods of the present technology may reduce body weight and/or fat mass in a subject in need thereof.

**[0223]** In some embodiments, the non-naturally occurring melanocortin analog is a non-naturally occurring melanocortin receptor antagonist and/or a melanocortin receptor agonist. The non-naturally occurring melanocortin analogs or the combinations comprising weight loss agents and non-naturally occurring melanocortin antagonists in accordance with the present technology may be useful in treating, preventing, reducing, or otherwise ameliorating one or more conditions, associated with a weight loss agent in a subject in need

thereof using non-naturally occurring melanocortin analogs. For example, combination therapies of the present technology may be useful in preventing or reducing lean mass loss (e.g., muscle, organ, and bone mass) associated with use of a weight loss agent in a subject in need thereof.

**[0224]** The present technology comprises methods of treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with metabolic dysfunction in a subject in need thereof using a non-naturally occurring melanocortin analog or a weight loss agent in combination with the non-naturally occurring melanocortin analog. In some embodiments, the method comprises suppressing appetite in a subject in need thereof using a combination comprising a non-naturally occurring melanocortin analog of the present technology or a weight loss agent in combination with the non-naturally occurring melanocortin analog. In some embodiments, the method comprises promoting fat loss in a subject in need thereof using a combination comprising a non-naturally occurring melanocortin analog of the present technology or a weight loss agent in combination with the non-naturally occurring melanocortin analog. In some embodiments, the method comprises reducing body weight and/or fat mass in a subject in need thereof using one or more a pharmaceutical compositions or the present technology.

**[0225]** The following description is merely exemplary in nature and is not intended to limit the present technology, its applications, or its uses. It should be understood that throughout the drawings, corresponding reference numerals indicate like or corresponding parts and features. The description of specific examples indicated in various embodiments of the present technology are intended for purposes of illustration only and are not intended to limit the scope of the present technology disclosed herein. Moreover, recitation of multiple embodiments having stated features is not intended to exclude other embodiments having additional features or other embodiments incorporating different combinations of the stated features.

**[0226]** Furthermore, the detailed description of various embodiments herein makes reference to the accompanying drawing/FIGS, which show various embodiments by way of illustration. While the embodiments are described in sufficient detail to enable those skilled in the art to practice the present technology, it should be understood that other embodiments

may be realized, and that logical changes may be made without departing from the spirit and scope of the present technology. Thus, the detailed description herein is presented for purposes of illustration only and not of limitation. For example, recited in any method or process may be executed in any order and are not limited to the order presented. Moreover, any of the steps thereof may be outsourced to or performed by one or more third parties.

### **Definitions**

**[0227]** Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the present technology belongs. For the purposes of the present technology, the following terms are defined below.

**[0228]** The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

**[0229]** The term “about” means a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by acceptable levels in the art. Typically, such variation may be as much 10% above and below a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length and such variation may be influenced by standard applicable measurement practices. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth.

**[0230]** The terms “administering” or “administer” include delivery of therapies (e.g., combination therapies, non-naturally occurring melanocortin analogs (also referred to herein as peptides and non-naturally occurring melanocortin analogs), of the present technology to a subject either by local or systemic administration. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer), intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or

intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration.

**[0231]** The terms “active ingredient” and “active compound” refer to a biologically active substance, whether naturally or non-naturally occurring, that is the main component of the pharmaceutical composition which elicits the intended effect of an administered therapeutic. This may be any component that drives the pharmacological activity or direct effect in the diagnosis, cure, mitigation, treatment, or prevention of the conditions associated with the present technology, such as but not limited to, reduced appetite and weight loss.

**[0232]** As used herein, a “composition” or a “pharmaceutical composition” refers to a mixture of the active ingredient with other chemical components, such as pharmaceutically acceptable carriers and/or excipients.

**[0233]** As used herein, a “pharmaceutically acceptable carrier” of the first or the second pharmaceutical composition refers to a carrier or diluent that does not cause significant irritation to an organism, does not abrogate the biological activity and properties of the administered active ingredient, and/or does not interact in a deleterious manner with the other components of the composition in which it is contained. The term “carrier” encompasses any excipient, binder, diluent, filler, salt, buffer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, e.g., Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005, which is incorporated herein by reference in its entirety). Some examples of physiologically acceptable carriers include antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN® (ICI, Inc.; Bridgewater, N.J.),

polyethylene glycol (PEG), and PLURONICS™ (BASF; Florham Park, N.J.). An “excipient” of the first or the second pharmaceutical composition refers to an inert substance added to a composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

**[0234]** The term “weight loss agent” refers to a therapeutic agent useful for the treatment or prevention of metabolic dysfunction or one or more symptoms associated with metabolic dysfunction in a subject. In some embodiments, such weight loss agents may be effective to treat, reduce, prevent, or otherwise be useful for a subject having a disease or condition that is not metabolic dysfunction, or besides metabolic dysfunction. The present technology is expected to be useful for subjects that may receive, have received, or are receiving one or more doses of a weight loss agent regardless of the underlying disease or condition that the subject has or develops.

**[0235]** The terms “treat”, “treatment”, and “treating” may also refer to the reduction or inhibition of the progression and/or duration of a disease (e.g., metabolic dysfunction), the reduction or amelioration of the severity of the disease, and/or the amelioration of one or more symptoms thereof resulting from the administration of one or more therapies. Specifically, these terms may refer to: (1) a stabilization or reduction (e.g. by more than 10%, 20%, 30%, 40%, 50%, or more than 60% of the baseline of glucose levels before administration) of circulating glucose levels (2) inhibiting or reducing rate of fat mass gain, (3) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with a pathology related to or caused in part by metabolic dysfunction, (4) an increase in disease-free, relapse-free, progression-free, and/or overall survival, duration, or rate, (5) a decrease in hospitalization rate, (6) a decrease in hospitalization length, (7) an increase in the oxidation of lipids or carbohydrates by at least by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, or at least 80% relative to the initial oxidation rate, (8) a stabilization or reduction (e.g. by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, or at least 80% relative to the initial loss rate) in the rate of lean muscle mass loss, (9) an increase in lean muscle mass, (10) a reduction in mortality, (11) an increase in the response rate, the durability of response, or number of patients who respond, (12) ) a stabilization or reduction (e.g. by more than 10%,

20%, 30%, 40%, 50%, or more than 60% of the baseline of lactate levels before administration) of circulating lactate levels, (13) a decrease in the need for surgery (e.g. gastric bypass, liposuction, sleeve gastrectomy, bariatric surgery), and (14) preventing or reducing organ burden induced by metabolic dysfunction. The terms “treat”, “treatment”, and “treating” include prophylactic and/or therapeutic treatments. If it is administered prior to clinical manifestation of a condition, the treatment is considered prophylactic. Therapeutic treatment includes, e.g., ameliorating or reducing the severity of a disease, or shortening the length or frequency of the disease.

**[0236]** As used herein, the term “prevent,” “preventing,” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

**[0237]** As used herein, the terms “effective amount” or “therapeutically effective amount”, refer to that amount of the active ingredient being administered which will relieve to some extent one or more of the symptoms of the disease being treated. The result may be a reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate “effective amount” may differ from one individual to another. An appropriate “effective amount” in any individual case may be determined using techniques, such as a dose escalation study.

**[0238]** The term “after administration” refers to any duration of time after the non-naturally occurring melanocortin analog or pharmaceutical composition thereof, and/or the weight loss agent has been administered to a subject. “After administration” may also refer to the duration of time after one dose has been completed or after more than one dose has been completed, such as two doses, three doses, four doses, and the like. In some embodiments, “after administration” refers to completion of dosing regimen that includes one or more doses. Likewise, the term “prior to administration” refers to any duration of time before the non-naturally occurring melanocortin analog or pharmaceutical composition thereof, and/or the weight loss agent has been administered to a subject. Unless otherwise

specified, durations of time encompassed by “after administration” or “prior to administration” may include seconds, minutes, hours, days, weeks, months, and years.

**[0239]** The term “Body Mass Index” or “BMI” refers to a value derived from an individual’s body weight and height. Specifically, BMI is determined by body weight (kilograms) divided by the square of height ( $m^2$ ) and is expressed in units of “kg/m<sup>2</sup>”. “Normal” BMI ranges are known to a person of ordinary skill in the art and consider factors such as patient sex, age, height, race, and body type. Typically, a normal BMI range is about 18.5 kg/m<sup>2</sup> to about 25 kg/m<sup>2</sup>.

**[0240]** The terms “subject” and “patient” refer to anyone being evaluated for disease or condition or being administered a therapeutic or pharmaceutical composition. This includes people without diagnosed or confirmed disease or condition. This also includes people with diagnosed or confirmed disease or condition, such as metabolic dysfunction.

**[0241]** The term “control subject,” as used herein, refers to any subject used as a basis for comparison to the subject (e.g., test subject). A control subject includes, but is not limited to, any subject who has not been administered the therapeutic or pharmaceutical composition (e.g., the non-naturally occurring melanocortin analog, a therapeutically effective amount of the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof) or administered a placebo. A control may reference to a measurement from the same subject as the subject being treated (e.g., a measurement at baseline or an intermediate timepoint), or from a different subject (e.g., a subject not having the same treatment or condition as the subject being treated).

**[0242]** “Melanocortin analogs,” “non-naturally occurring melanocortin analogs,” “melanocortin peptides,” “melanocortin receptor peptides,” or “melanocortins,” are used interchangeably and refer to melanocortin-receptor ligands, which are macromolecules containing at least one melanocortin pharmacophore. Melanocortin analogs are typically peptides that bind melanocortin receptors under physiological conditions. Melanocortin analogs include naturally occurring non-naturally occurring melanocortin analogs (i.e., “synthetic peptides” or “synthetic analogs”) and truncated and/or modified versions of melanocortin full-length protein or peptides. For example, the full-length pro-opiomelanocortin protein (POMC), prior to proteolytic cleavage of “sub-peptides,” consists

of 241 amino acids. Tissue-specific proteolytic cleavage of POMC yields peptides ranging in size from 13 amino acids to 76 amino acids. See Bicknell and Lawry, *Encyclopedia of Stress*, vol. 3, 257-265, Academic Press (2000). Synthesized, non-naturally occurring melanocortin analogs having increased melanocortin receptor activity as discussed herein are approximately 7-12 amino acids in size. Melanocortin analogs exhibit binding functionality with melanocortin receptors. The binding to the melanocortin receptor is inhibitory (antagonist). In addition to peptides, the non-naturally occurring melanocortin analogs include small molecule analogs of melanocortin or portions thereof comprised of organic compounds, inorganic compounds, or combinations of peptide and small molecule—i.e., peptide mimetics, or various combinations thereof. “Non-naturally occurring melanocortin analogs” may be structurally similar and/or functionally similar to biological melanocortin proteins in their ability to bind melanocortin receptors. Further, the non-naturally occurring melanocortin analogs generally contain the pharmacophore: His-Phe-Arg-Trp (SEQ ID NO: 1) or a modified version thereof, or a structural or functional peptide mimetic thereof.

**[0243]** A “pharmacophore” is the minimum set of amino acid residues necessary to achieve a physiological effect; or a small molecule that is (with respect to a receptor) a structural mimic of the amino acid residues required for binding to and activation of a receptor. His-Phe-Arg-Trp (SEQ ID NO: 1) and their analogs are the pharmacophore of melanocortin for the regulated physiological effect. Therefore, non-naturally occurring melanocortin pharmacophore analogs may be small peptides or organic molecules designed to mimic the appearance or function (including activation or deactivation of receptor activity) of the melanocortin pharmacophore core sequence peptide.

**[0244]** A “melanocortin receptor agonist” or “melanocortin agonist” is a naturally occurring substance or manufactured drug substance or composition that may interact with a melanocortin receptor and initiate a pharmacological response characteristic of the melanocortin receptor.

**[0245]** The terms “bind,” “binding,” “complex,” and “complexing,” refer to all types of physical and chemical binding, reactions, complexing, attraction, chelating and the like.



**[0246]** The “peptides” of the present technology may be (a) naturally occurring, (b) produced by chemical synthesis, (c) produced by recombinant DNA technology, (d) produced by biochemical or enzymatic fragmentation of larger molecules, (e) produced by methods resulting from a combination of methods (a) through (d) listed above, or (f) produced by any other means for producing peptides.

**[0247]** The term “peptide” as used herein includes any structure comprised of two or more amino acids, including chemical modifications and derivatives of amino acids. The amino acids forming all or a part of a peptide may be naturally occurring amino acids, stereoisomers and modifications of such amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically modified amino acids, constructs or structures designed to mimic amino acids, and the like, so that the term “peptide” includes pseudopeptides and peptidomimetics, including structures which have a non-peptidic backbone. The term “peptide” also includes dimers or multimers of peptides. A “manufactured” peptide includes a peptide produced by chemical synthesis, recombinant DNA technology, biochemical, or enzymatic fragmentation of larger molecules, combinations of the foregoing or, in general, made by any other method. The term “peptide” includes peptides containing a variable number of amino acid residues, optionally with non-amino acid residue groups at the N- and C-termini, such groups including acyl, acetyl, alkenyl, alkyl, N-alkyl, amine, or amide groups, among others.

**[0248]** By employing chemical synthesis, a useful means of production, it is possible to introduce various amino acids which do not naturally occur along the chain, modify the N- or C-terminus, and the like, thereby providing for improved stability and formulation, resistance to protease degradation, and the like.

**[0249]** “Amino acids” are molecules containing an amine group, a carboxylic acid group, and a side-chain that is specific to each amino acid. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen and have the generic formula  $\text{H}_2\text{N}-\text{CHR}-\text{COOH}$ , wherein R represents a side chain group. The various  $\alpha$ -amino acids differ in the side-chain moiety that is attached to the  $\alpha$ -carbon. The “amino acids” of the present technology include the known naturally occurring protein amino acids, which are referred to by both their common three letter abbreviation and single letter abbreviation. See

generally *Synthetic Peptides: A User's Guide*, G. A. Grant, editor, W.H. Freeman & Co., New York (1992), the teachings of which are incorporated herein by reference, including the text and table set forth at pages 11 through 24. As set forth above, the term “amino acid” also includes stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, and the like. Modified and unusual amino acids are described generally in *Synthetic Peptides: A User's Guide*, supra; Hruby et al., *Biochem. J.* 268:249-262 (1990); and Toniolo, *Int. J. Peptide Protein Res.* 35:287-300 (1990); the teachings of all of which are incorporated herein by reference.

**[0250]** The phrase “amino acid side chain moiety” used herein, including as used in the specification and claims, includes any side chain of any amino acid, as the term “amino acid” is defined herein. This thus includes the side chain moiety present in naturally occurring amino acids. It further includes side chain moieties in modified naturally occurring amino acids, such as glycosylated amino acids. It further includes side chain moieties in stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs, or structures designed to mimic amino acids, and the like. For example, the side chain moiety of any amino acid disclosed herein is included within the definition. A “derivative” of an amino acid side chain moiety is included within the definition of an amino acid side chain moiety.

**[0251]** The “derivative” of an amino acid side chain moiety includes any modification to or variation in any amino acid side chain moieties, including a modification of naturally occurring amino acid side chain moieties. By way of example, derivatives of amino acid side chain moieties include straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated, alkyl, aryl or aralkyl moieties.

**[0252]** In the peptides of the present technology, conventional amino acid residues have their conventional meaning as given in Chapter 2400, of the Manual of Patent Examining Procedure, 8th Ed. Thus, “Ala” is alanine; “Arg” is arginine; “Asn” is asparagine; “Asp” is aspartic acid; “Cys” is cysteine; “Gln” is glutamine; “Glu” is glutamic acid; “His” is

histidine; "Ile" is isoleucine; "Leu" is leucine; "Lys" is lysine; "Met" is methionine; "Phe" is phenylalanine; "Pro" is proline; "Ser" is serine; "Thr" is threonine; "Trp" is tryptophan; "Tyr" is tyrosine; and "Val" is valine. Unless otherwise indicated, all amino acids abbreviations represent either isomer, i.e., the L-isomer, the D-isomer, or combinations thereof may be used. Thus, for example, "L-Phe" or "lPhe" is L-phenylalanine; "D-Phe" or "dPhe" is D-phenylalanine; dVal is D-valine; dPro is D-proline; "D-/L-Phe" or "d/lPhe" is D-phenylalanine, L-phenylalanine, or combinations thereof; "Phe" is also D-phenylalanine, L-phenylalanine, or combinations thereof, and so on.

**[0253]** An alpha ( $\alpha$ )-amino acid has the generic formula  $\text{H}_2\text{N}-\text{C}\alpha\text{HR}-\text{COOH}$ , where R is a side chain moiety and the amino group is attached to the carbon atom immediately adjacent to the carboxylate group (i.e., the  $\alpha$ -carbon). Other types of amino acids exist when the amino group is attached to a different carbon atom. For example, beta ( $\beta$ )-amino acids, the carbon atom to which the amino group is attached is separated from the carboxylate group by one carbon atom,  $\text{C}\beta$ .

**[0254]** When  $\beta$ -amino acids are incorporated into peptides, two main types of  $\beta$ -peptides exist: those with the side chain residue, R, on the carbon next to the amine are called  $\beta_3$  peptides and those with the side chain residue on the carbon next to the carbonyl group are called  $\beta_2$  amino acids.

**[0255]** Gamma ( $\gamma$ )-amino acids are amino acids with the carbon atom to which the amino group attaches is separated from the carboxylate moiety by two carbon atoms.

**[0256]** For additional modified and unusual amino acids, see §2422 of the MPEP, particularly Table 4 at 2400-24. Additionally, "Ac" indicates N-acetyl and "cyclo" refers to a cyclic structure, which is also shown as "c." "NH<sub>2</sub>" indicates an amine group, typically added on the C-terminus of a polypeptide. Accordingly, as used herein, an —NH<sub>2</sub> moiety on the C-terminus of a peptide indicates an amidated C-terminus. In addition, the following abbreviations are used herein: Nle is norleucine; Nal(2') is 2'-naphthylalanine; Nal(1') is 1'-naphthylalanine; Tle is tert-leucine; Nva is norvaline; Orn is ornithine; Bip is biphenylalanine; Hyp is hydroxyproline; Mamb is 3-aminomethyl-benzoic acid; Pen is Penicillamine; Tic is 1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid; Aba is 4-amino-1,2,4,5-tetra-hydro-2-benzazepin-3-one; Oic is octahydroindole-2-carboxylic acid; Atc is 2-aminotetraline-2-

carboxylic acid; APC is 1-amino-4-phenylcyclohexane-carboxylic acid; APPC is 4-aminophenylpiperidine-4-carboxylic acid; Acpc is 1-aminocyclo-propane-1-carboxylic acid; Aic is 2-aminoindone-2-carboxylic acid; Ata is 7-amino-7,8-dihydro-4H-[1,2,3]triazolo-[1,5-a][1,4]diazepin-6(5H)-one; Aia is 4-amino-1,4,5,6-tetrahydroazepino[4,3-*b*]indol-3(2*H*)-one; Che is 1-amino-1-cyclohexanecarboxylic acid Ioc is indoline-2-carboxylic acid, Aic is 2-aminoindone-2-carboxylic acid; Cpe is 1-amino-1-cyclopentane carboxylic; and p(Cl)dPhe is para-chloro-phenylalanine (I – iodo, F – fluoro, Br – bromo, CF<sub>3</sub> – trifluoromethyl).

**[0257]** The term “acyl” includes a group RCO—, where R is an organic group. An example is the acetyl group CH<sub>3</sub>CO—, referred to herein as “Ac.”

**[0258]** A peptide or aliphatic moiety is “acylated” when an alkyl or substituted alkyl group as defined above is bonded through one or more carbonyl {—(C=O)—} groups. A peptide is most usually acylated at the N-terminus.

**[0259]** An “amine” includes compounds that contain an amine group (—NH<sub>2</sub>).

**[0260]** An “amide” includes compounds that have a trivalent nitrogen attached to a carbonyl group (i.e., —CO—NH<sub>2</sub>), such as for example methylamide, ethylamide, propylamide, and the like. A peptide is most usually amidated at the C-terminus by the addition of an amine (—NH<sub>2</sub>) moiety to the C-terminal carboxyl group.

**[0261]** Amino acids, including stereoisomers and modifications of naturally occurring amino acids, protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs, or structures designed to mimic amino acids (peptide mimetics), and the like, including all of the foregoing, are sometimes referred to herein as “residues.”

**[0262]** “Substantial degradation” refers to the degradation of the N-terminal extension, the C-terminal extension, both N- and C-terminal degradation or degradation to other regions of the non-naturally occurring melanocortin analog by physiological enzymes and other factors, in such a manner or to a degree that side effects appear. According to one aspect, a non-naturally occurring melanocortin analog having a C-terminal extension that resists substantial degradation is one where no more than 50% of the administered peptide causes side effects and/or displays a low half-life. In some aspects, no more than 25% of the

administered peptide causes side effects and/or displays a low half-life. More preferably, in some aspects, less than 10% of the administered peptide causes side effects and/or displays a low half-life, as compared to a non-naturally occurring melanocortin analog that lacks a C-terminal extension.

**[0263]** As used herein, a “composition” refers to a mixture of the active ingredient with other chemical components.

**[0264]** The disclosure of all publications, patents, and published patent applications listed herein are hereby incorporated by reference in their entireties, including but not limited to U.S. Patent Nos. 8,541,545 and 9,534,018.

***Non-naturally Occurring Melanocortin Analogs***

**[0265]** The non-naturally occurring melanocortin analogs of the present technology may comprise a non-naturally occurring melanocortin analog or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. Non-naturally occurring melanocortin analogs of the present technology may be selective for the melanocortin 4 receptor (MC4R) and/or melanocortin 3 receptor (MC3R) over other melanocortin receptors, i.e., the melanocortin 1 receptor (MC1R), the melanocortin 2 receptor (MC2R), and the melanocortin 5 receptor (MC5R). Some of the non-naturally occurring melanocortin analogs may bind the MC4R with greater affinity than the MC3R. Alternatively, some melanocortin analogs may bind the MC3R with the same or generally similar affinity as the MC4R.

**[0266]** The non-naturally occurring melanocortin analogs of the present technology may be full agonists for one or more melanocortin receptors. A full agonist may comprise a non-naturally occurring melanocortin analog having a maximum effect ( $E_{\max}$ ) agonist value of greater than or equal to 85%.

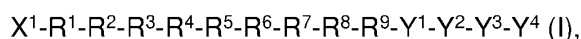
**[0267]** The non-naturally occurring melanocortin analogs of the present technology may be partial agonists. A partial agonist may comprise a non-naturally occurring melanocortin analog having a maximum effect  $E_{\max}$  agonist value of less than 85%.

**[0268]** If a non-naturally occurring melanocortin analog's  $E_{\max}$  agonist value is greater than its  $E_{\max}$  antagonist value, then the non-naturally occurring melanocortin analog may be classified as an agonist (e.g., a full agonist or a partial agonist).

**[0269]** The non-naturally occurring melanocortin analogs of the present technology may be one or more of (i) a full MC4R agonist (ii) a full MC3R agonist; and (iii) a partial MC3R agonist with no MC3R antagonist activity. In some embodiments, the non-naturally occurring melanocortin is a full MC4R agonist. In some embodiments, the non-naturally occurring melanocortin agonist is a full MC3R agonist and a full MC4R agonist. In some embodiments, the non-naturally occurring melanocortin analog is a full MC4R agonist and partial MC3R agonist with no MC3R antagonist activity. In some embodiments, the non-naturally occurring melanocortin analogs of the present technology have an MC3R  $E_{\max}$  agonist value of 50-84%. In some embodiments, the non-naturally occurring melanocortin analogs of the present technology have a MC3R:MC4R half maximal effective concentration ( $EC_{50}$ ) selectivity ratio of less than or equal to 49. In some embodiments, the non-naturally occurring melanocortin analogs of the present technology comprise non-naturally occurring MC4R agonists or non-naturally occurring MC3R agonists.

**[0270]** The non-naturally occurring melanocortin analogs in accordance with the present technology may have certain structural features that impart specific properties on the analogs, such as, for example, degradation resistance, enhanced epithelial, gastrointestinal, and/or blood brain barrier transport, and binding affinity for the melanocortin 4 receptor and/or melanocortin 3 receptor. Accordingly, in some embodiments, the non-naturally occurring melanocortin analogs have one or more beta hairpin ( $\beta$ -hairpin) and/or beta turn ( $\beta$ -turn) structures. The presence of amino acids that are structurally rigid, such as, for example, Aia, Aba, Ata, Hyp, dHyp, Pro, dPro, transPro(guan), and cisPro(guan), may lead to formation of  $\beta$ -hairpin and/or  $\beta$ -turn structures in the non-naturally occurring melanocortin analog. Additionally, dMet and disulfide bridges (e.g., cyclization via disulfide bond), as well as Pro-Gly and Gly-Gly linkers may induce and/or stabilize beta-turn structures of the non-naturally occurring melanocortin analogs. In general, cyclization may stabilize beta-turns, and D-amino acids may induce and/or stabilize beta-turns. Further, in some embodiments, melanocortin analogs include D-valine-D-proline (dVal-dPro) chain as their C-terminus, which may provide enhanced transport and resistance to degradation.

**[0271]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I):



wherein:

$X^1$  is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

$R^1$  is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

$R^2$  is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

$R^3$  is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

$R^4$  is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

$R^5$  is selected from the group consisting of His, Arg, *cis*-4-guanidinyI-proline (*cis*Pro(guan)), and *trans*-4-guanidinyI-proline (*trans*Pro(guan));

$R^6$  is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

$R^7$  is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

$R^8$  is absent, Lys, or Trp;

$R^9$  is absent or Lys;

$Y^1$  is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

$Y^2$  is selected from the group consisting of dVal, dPro, and dTle;

$Y^3$  is absent, dVal, or dPro;

$Y^4$  is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys; provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

**[0272]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I), wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));



R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;

R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac-Nle-c[Asp-Phe-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 366);

Ac-Nle-c[Asp-Phe-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 412);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 423);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 424);

Ac-Nle-c[Asp-Phe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 487);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 225);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231);

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302);  
His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 306);  
dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 309);  
Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 311);  
Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 312);  
Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 313);  
Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 314);  
Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 315);  
Ac-Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 413);  
Ac-Nle-c[Asp-dHis-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 416);  
Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 425);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436);  
Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 437);  
Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 438);  
Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 439);  
Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 440);  
Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 441);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 443);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 447);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453);  
Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 454);  
Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 455);  
Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 456);  
Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 457);  
Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 458);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 597);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 598);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 642);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 643);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 644);

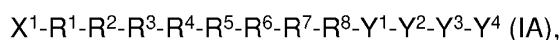
Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 645);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 646);

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); and

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[0273]** In some embodiments, R<sup>9</sup> is absent. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA):



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, Ala, and D-alanine (dAla);

R<sup>3</sup> is His or dHis;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is His or Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Pro or lysine (Lys);

R<sup>8</sup> is absent or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is dVal or dPro;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp and R<sup>7</sup> or R<sup>8</sup> is Lys;

provided that when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

**[0274]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA), wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, Ala, and D-alanine (dAla);

R<sup>3</sup> is His or dHis;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is His or Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Pro or lysine (Lys);

R<sup>8</sup> is absent or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is dVal or dPro;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp and R<sup>7</sup> or R<sup>8</sup> is Lys;

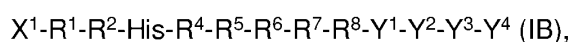
provided that the non-naturally occurring melanocortin analog does not comprise the sequence:

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[0275]** In some embodiments, R<sup>3</sup> is His. In further embodiments, R<sup>3</sup> and R<sup>4</sup> form the moiety His-p(X)dPhe, where X is H or F. In still further embodiments, R<sup>3</sup> and R<sup>4</sup> form the moiety His-dPhe or His-p(F)dPhe.

**[0276]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB):



wherein:

X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is Asp;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is Pro or Lys;

R<sup>8</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>2</sup> is Asp, and R<sup>7</sup> or R<sup>8</sup> is Lys;

**[0277]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB), wherein:  
wherein:

X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is Asp;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is His or Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Pro or Lys;

R<sup>8</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is dVal or dPro;

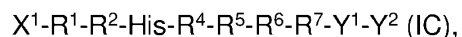
Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>2</sup> is Asp, and R<sup>7</sup> or R<sup>8</sup> is Lys.

**[0278]** In some embodiments, R<sup>3</sup> is His and R<sup>4</sup> is dPhe. In further embodiments, R<sup>2</sup> is Ala or dAla. In still further embodiments, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup>, form the moiety Ala-His-dPhe or dAla-His-dPhe.

**[0279]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC):



wherein:

X<sup>1</sup> is norleucine (Nle), arginine (Arg) or D-arginine (dArg);

R<sup>1</sup> is aspartic acid (Asp);

R<sup>2</sup> is alanine (Ala) or D-alanine (dAla);

R<sup>4</sup> is D-phenylalanine (dPhe);

R<sup>5</sup> is Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Lys;

Y<sup>1</sup> is D-valine (dVal);

Y<sup>2</sup> is D-proline (dPro); and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R<sup>2</sup> and Lys at R<sup>7</sup>;

provided that when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

**[0280]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC), wherein:

X<sup>1</sup> is norleucine (Nle), arginine (Arg) or D-arginine (dArg);

R<sup>1</sup> is aspartic acid (Asp);

R<sup>2</sup> is alanine (Ala) or D-alanine (dAla);

R<sup>4</sup> is D-phenylalanine (dPhe);

R<sup>5</sup> is Arg;



R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Lys;

Y<sup>1</sup> is D-valine (dVal);

Y<sup>2</sup> is D-proline (dPro); and

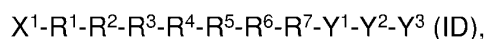
the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R<sup>2</sup> and Lys at R<sup>7</sup>;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence of:

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[0281]** In some embodiments, R<sup>8</sup> is absent. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID):



wherein:

X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro);

R<sup>3</sup> is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro);

R<sup>4</sup> is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is cysteine (Cys) or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys; and

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> is Lys;

provided that:

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present, or (ii) X<sup>1</sup> and Y<sup>3</sup> are absent, R<sup>1</sup> is Nle, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated;

when R<sup>4</sup> is dPhe, then (i) R<sup>3</sup> is not His or Gln or (ii) R<sup>3</sup> is His and either R<sup>2</sup> is Pro or R<sup>5</sup> is transPro(guan) or cisPro(guan); and

when R<sup>4</sup> is p(F)dPhe, R<sup>3</sup> is His, and R<sup>1</sup> is Nle, then (i) R<sup>6</sup> is not Trp or (ii) Y<sup>3</sup> is dVal.

**[0282]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID), wherein:

X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro);

R<sup>3</sup> is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro);

R<sup>4</sup> is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of Arg, *cis*-4-guanidinyl-proline (*cis*Pro(guan)), and *trans*-4-guanidinyl-proline (*trans*Pro(guan));

R<sup>6</sup> is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is cysteine (Cys) or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys; and

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 225);

Ac-Nle-c[Asp-Pro-dPhe-*trans*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231);

Ac-Nle-c[Asp-Pro-dPhe-*cis*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435);

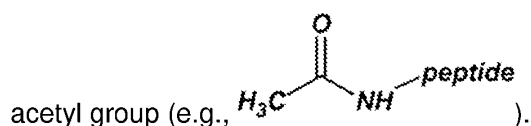
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641);  
Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363);  
Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370);

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223);  
 Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 476);  
 Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and  
 Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478).

**[0283]** In some embodiments, the non-naturally occurring melanocortin analog of any one of Formulae (I)-(ID) has one or more beta hairpin ( $\beta$ -hairpin) and/or beta turn ( $\beta$ -turn) structures. In some embodiments, the presence of Pro, *cis*Pro(guan) and/or *trans*Pro(guan) in the melanocortin analog provides the  $\beta$ -hairpin and/or  $\beta$ -turn structures of the non-naturally occurring melanocortin analog. In some embodiments, the disulfide bond of the sequence according to Formula (I), if present, provides the  $\beta$ -hairpin and/or  $\beta$ -turn structures of the non-naturally occurring melanocortin analog.

**[0284]** As will be appreciated by the skilled artisan, non-naturally occurring melanocortin analogs comprising a sequence of any one of Formulae (I)-(ID), have an N-terminus and a C-terminus. The melanocortin analogs of the present technology are written beginning with the N-terminus at the left-most amino acid residue and ending with the C-terminus at the right most residue. Accordingly, the N-terminus of a non-naturally occurring melanocortin analog comprising a sequence of any one of Formulae (I)-(ID) may be at X<sup>1</sup> or R<sup>1</sup>. Analogously, the C-terminus of a non-naturally occurring melanocortin analog comprising a sequence of any one of Formulae (I)-(ID) may be at any of R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup>, and Y<sup>4</sup>.

**[0285]** In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog is modified by an acyl group. In some embodiments, the acyl group is



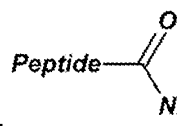
**[0286]** In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog is not modified.

**[0287]** In the sequence of any one of Formulae (I)-(ID),  $Y^1Y^2Y^3Y^4$  represents a C-terminus of the non-naturally occurring melanocortin analog. In some embodiments,  $Y^1$  and  $Y^2$  are present and  $Y^3$ - $Y^4$  are absent. In some embodiments,  $Y^3$ - $Y^4$  are absent, and  $Y^1$  is D-valine and  $Y^2$  is D-proline. In some embodiments,  $Y^3$ - $Y^4$  are absent, and  $Y^1$  is D-proline and  $Y^2$  is D-valine. In some embodiments,  $Y^3$ - $Y^4$  are absent, and  $Y^1$  is D-tert-leucine and  $Y^2$  is D-proline.

**[0288]** In some embodiments,  $Y^1$ - $Y^3$  are present and  $Y^4$  is absent. In some embodiments,  $Y^4$  is absent and (i)  $Y^1$  is D-proline, (ii)  $Y^2$  is D-valine, and (iii)  $Y^3$  is D-proline. In some embodiments,  $Y^4$  is absent, and (i)  $Y^1$  is D-tert-leucine,  $Y^2$  is D-tert-leucine, and  $Y^3$  is D-valine.

**[0289]** In some embodiments,  $Y^1$ - $Y^4$  are present. In some embodiments,  $Y^1$ - $Y^4$  are present and (i)  $Y^1$  is D-valine, (ii)  $Y^2$  is D-valine, (iii)  $Y^3$  is D-valine, and (iv)  $Y^4$  is D-proline.

**[0290]** In some embodiments, the C-terminus of the non-naturally occurring



melanocortin analog is modified by an amide group (e.g., In the sequence of Formula (I), a non-naturally occurring melanocortin analog with a C-terminus modified by an amide may be represented by a terminal -NH<sub>2</sub>.

**[0291]** In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is not modified. In the sequence of Formula (I), a non-naturally occurring melanocortin analog with an unmodified C-terminus may be represented by -OH.

**[0292]** Non-naturally occurring melanocortin analogs comprising a sequence of any one of Formulae (I)-(ID) are cyclized. For example, the non-naturally occurring melanocortin analog may be cyclized through a moiety selected from the group consisting of: a disulfide bond between  $R^2$  and  $R^7$  when  $R^2$  is dCys,  $R^4$  is p(Cl)dPhe, and  $R^7$  is Cys; a lactam bridge between  $R^1$  or  $R^2$  and  $R^7$  or  $R^8$  when  $R^1$  or  $R^2$  is Asp,  $R^4$  is dPhe or p(F)dPhe, and  $R^7$  or  $R^8$  is Lys; and a lactam bridge between  $R^1$  and  $R^9$  when  $R^1$  is Asp,  $R^6$  is dPhe, and  $R^9$  is Lys.

**[0293]** In some embodiments of the sequence of Formulae (I)-(ID), R<sup>3</sup> is His. In some embodiments, when R<sup>3</sup> is His, then X<sup>1</sup> is absent and R<sup>1</sup> is present. In some embodiments, R<sup>1</sup> is norleucine. In further embodiments, R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, and R<sup>7</sup> is Lys. In some embodiments, Y<sup>1</sup> and Y<sup>2</sup> are each independently dVal or dPro. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 476);

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363); and

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0294]** Alternatively, in some embodiments, R<sup>1</sup> is an amino acid other than norleucine. In some embodiments, R<sup>1</sup> is selected from Ala, Arg, dArg, Lys, dLys, His, or dHis. In further embodiments, R<sup>2</sup> is Asp, R<sup>4</sup> is p(F)dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, and R<sup>7</sup> is Lys. In some embodiments, Y<sup>1</sup> is dVal and Y<sup>2</sup> is dPro. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 462);

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 463);

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 464);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 465);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 466);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 467); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 468),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0295]** In some embodiments, R<sup>1</sup> is selected from Arg, Lys, dLys, His, or dHis. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 464);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 465);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 466);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 467); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 468),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0296]** In some embodiments, R<sup>1</sup> is Ala or dArg. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 462); or

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 463),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0297]** In some embodiments, Y<sup>1</sup> is dTle and Y<sup>2</sup> is dPro. In some embodiments, the sequence of any one of Formula (I)-(ID) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 479);

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 480);

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 481);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 482);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 483);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 484); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 485),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.



**[0298]** In some embodiments, R<sup>1</sup> is selected from Arg, Lys, dLys, His, or dHis. In some embodiments, the sequence of any one of Formula (I)-(ID) is selected from the group consisting of:

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 481);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 482);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 483);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 484); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 485),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0299]** In some embodiments, R<sup>1</sup> is Ala or dArg. In some embodiments, the sequence of any one of Formulae (I)-(ID) is:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 479); or

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 480),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0300]** . In some embodiments, when R<sup>3</sup> is His, then X<sup>1</sup> and R<sup>1</sup> are present. In some embodiments, when X<sup>1</sup> and R<sup>1</sup> are present, then R<sup>2</sup> is Ala or dAla. In some embodiments, X<sup>1</sup> is Nle or dArg, R<sup>1</sup> is Asp, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, and R<sup>7</sup> is Lys. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 268);

Ac-Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 378);

Ac-dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 379); and

Ac-Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 380),

wherein c represents cyclization through R<sup>1</sup> and R<sup>7</sup> via a lactam bond.

**[0301]** In some embodiments, when R<sup>3</sup> is His, then at least one of X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are present. In some embodiments, X<sup>1</sup> is absent. In other embodiments, X<sup>1</sup> is Nle. In some

embodiments, Y<sup>3</sup>-Y<sup>4</sup> are absent. In some embodiments, Y<sup>3</sup> is dVal or dPro and Y<sup>4</sup> is absent. In some embodiments, Y<sup>3</sup> is dVal and Y<sup>4</sup> is dPro. In some embodiments, R<sup>2</sup> is Asp, R<sup>4</sup> is p(F)dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, and R<sup>7</sup> is Lys. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 473);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 474);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475);  
 Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and  
 Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478),  
 wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0302]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 474);  
 Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475);  
 Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and  
 Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478),  
 wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0303]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 473), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0304]** In some embodiments, when R<sup>3</sup> is His, then R<sup>5</sup> is Arg. Alternatively, in some embodiments, R<sup>5</sup> is an amino acid other than Arg. In some embodiments, R<sup>5</sup> is selected from His, *trans*Pro(guan) and *cis*Pro(gaun). In further embodiments, R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe

or p(F)dPhe, R<sup>6</sup> is Trp, and R<sup>7</sup> is Lys. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-His-dPhe-*trans*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 228);

Ac-Nle-c[Asp-His-dPhe-*cis*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 229); and

Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 470),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0305]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is:

Ac-Nle-c[Asp-His-dPhe-*trans*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 228) or

Ac-Nle-c[Asp-His-dPhe-*cis*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 229),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0306]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 470), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0307]** In some embodiments, when R<sup>3</sup> is His, then R<sup>6</sup> is Trp. Alternatively, in some embodiments, R<sup>6</sup> is an amino acid other than Trp. In some embodiments, R<sup>6</sup> is dNal(2'). In some embodiments, the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 471), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0308]** In some embodiments of the sequence of any one of Formula (I)-(ID), R<sup>3</sup> is an amino acid other than His. In some embodiments, R<sup>3</sup> is selected from dHis, Gln and Pro. In further embodiments, R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, R<sup>6</sup> is Trp, and R<sup>7</sup> is Lys. In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 365);

Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370);

Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 486);

Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 491); and  
 Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 639),  
 wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0309]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 365);  
 Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370); and  
 Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 486),  
 wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0310]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is:

Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 491); or  
 Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 639),  
 wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0311]** In some embodiments of the sequence of any one of Formulae (I)-(ID), the non-naturally occurring melanocortin analog is cyclized through R<sup>2</sup> and R<sup>7</sup> via a lactam bond. In other embodiments, the non-naturally occurring melanocortin analog is cyclized through R<sup>2</sup> and R<sup>7</sup> via a disulfide bond. In some embodiments, the sequence of any one of Formulae (I)-(ID): Ac-Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 498), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a disulfide bond.

**[0312]** In other embodiments, the non-naturally occurring melanocortin analog is cyclized through R<sup>1</sup> and R<sup>7</sup> or R<sup>2</sup> and R<sup>8</sup> via a lactam bond. In some embodiments, either R<sup>2</sup> or R<sup>7</sup> is Pro. In further embodiments, R<sup>1</sup> Nle or Asp, R<sup>2</sup> is Asp or Pro, R<sup>3</sup> is His, R<sup>4</sup> is dPhe, R<sup>6</sup> is Trp, and R<sup>7</sup> is Lys or Pro and R<sup>8</sup> is absent or Lys. In some embodiments, the sequence of any one of Formulae (I)-(ID) is:

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 297); or  
 Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 418).

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0313]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 297), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

**[0314]** In some embodiments, the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 418), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

In some embodiments of the sequence of Formula (I), R<sup>9</sup> is absent. Alternatively, in some embodiments, R<sup>9</sup> is present. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of: Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 420), wherein c represents cyclization through R<sup>1</sup> and R<sup>9</sup> via a lactam bond.

**[0315]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498.

**[0316]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486.

**[0317]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621.

**[0318]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC). In some embodiments, the non-naturally occurring

melanocortin analog comprises any one of the sequences of SEQ ID NOs: 268 and 378-380.

**[0319]** In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0320]** Non-naturally occurring melanocortin analog of any one of Formulae (I)-(ID) may be an agonist of the melanocortin 4 receptor and an agonist of the melanocortin 3 receptor. In some embodiments, non-naturally occurring melanocortin analogs of any one of Formulae (I)-(ID) are full agonists of the melanocortin 4 receptor and full agonists of the melanocortin 3 receptor. In other embodiments, non-naturally occurring melanocortin analogs of any one of Formulae (I)-(ID) are full agonists of the melanocortin 4 receptor and partial agonists of the melanocortin 3 receptor.

*Non-Naturally Occurring Melanocortin Analog Synthesis*

**[0321]** The non-naturally occurring melanocortin analogs of the present technology may be readily synthesized by any known conventional procedure for the formation of a peptide linkage between amino acids. Such conventional procedures include, for example, any solution phase procedure permitting a condensation between the free alpha amino group of an amino acid or residue thereof having the carboxyl group or other reactive groups protected and the free primary carboxyl group of another amino acid or residue thereof having the amino group or other reactive groups protected. In an exemplary procedure, the peptides of the present technology may be synthesized by solid-phase synthesis and purified according to methods known in the art. Any of a number of well-known procedures utilizing a variety of resins and reagents may be used to prepare the peptides of the present technology.

**[0322]** The process for synthesizing the peptides may be carried out by a procedure whereby each amino acid in the desired sequence is added one at a time in succession to another amino acid or residue thereof or by a procedure whereby peptide fragments with

the desired amino acid sequence are first synthesized conventionally and then condensed to provide the desired peptide. The resulting peptide is then cyclized to yield a cyclic peptide.

**[0323]** Solid phase peptide synthesis methods are well known and practiced in the art. In such methods, the synthesis of peptides may be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods. These methods are disclosed in numerous references, including Merrifield, *Angew Chem.* 24:799-810 (1985) and Barany et al., *The Peptides, Analysis, Synthesis and Biology*, Vol. 2, Gross E. and Meienhofer J., Eds. Academic Press 1-284 (1980).

**[0324]** In chemical syntheses of peptides, reactive side chain groups of the various amino acid residues are protected with suitable protecting groups, which prevent a chemical reaction from occurring at that site until the protecting group is removed. Also common is the protection of the alpha amino group of an amino acid residue or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site. Specific protecting for solid phase synthesis methods and solution phase synthesis methods groups are known to those having ordinary skill in the art.

**[0325]** Alpha amino groups may be protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. Fmoc is useful for alpha amino protection.

**[0326]** Guanidino groups may be protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tosyl), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc is a useful protecting group for Arg.

**[0327]** Solid phase synthesis is commenced from the C-terminal end of the peptide by coupling a protected alpha amino acid to a suitable resin. Such starting material is prepared by attaching an alpha amino-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin or a 2-chlorotrityl chloride resin, by an amide bond between an Fmoc-Linker, such as p-[(R,S)- $\alpha$ -[1-(9H-fluor-en-9-yl)-methoxyformamido]-2,4-dimethyloxybenzyl]-phenoxyacetic acid (Rink linker) to a benzhydrylamine (BHA) resin, or by other means well known in the art. Fmoc-Linker-BHA resin supports are commercially available and generally used when feasible. The resins are carried through repetitive cycles as necessary to add amino acids sequentially. The alpha amino Fmoc protecting groups are removed under basic conditions. Piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF) may be used for this purpose.

**[0328]** Following removal of the alpha amino protecting group, the subsequent protected amino acids are coupled stepwise in the desired order to obtain an intermediate, protected peptide-resin. The activating reagents used for coupling of the amino acids in the solid phase synthesis of the peptides are well known in the art. After the peptide is synthesized, if desired, the orthogonally protected side chain protecting groups may be removed using methods well known in the art for further derivatization of the peptide.

**[0329]** Reactive groups in a peptide may be selectively modified, either during solid phase synthesis or after removal from the resin. For example, peptides may be modified to obtain N-terminus modifications, such as acetylation, while on resin, or may be removed from the resin by use of a cleaving reagent and then modified. Methods for N-terminus modification, such as acetylation, and for C-terminus modification, such as amidation, are known in the art. Similarly, methods for modifying side chains of amino acids are well known to those skilled in the art of peptide synthesis. The choice of modifications made to reactive groups present on the peptide will be determined, in part, by the characteristics that are desired in the peptide.

**[0330]** The peptide may be cyclized prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains are deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents include, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone



(NMP). Suitable cyclic coupling reagents include, for example, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1 (2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or N,N'-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt). Coupling is convention initiated by use of a suitable base, such as N,N-diisopropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

**[0331]** Following cleavage of peptides from the solid phase following their synthesis, the peptide may be purified by any number of methods, such as reverse phase high performance liquid chromatography (RP-HPLC), using a suitable column, such as a C18 column. Other methods of separation or purification, such as methods based on the size or charge of the peptide, may also be employed. Once purified, the peptide may be characterized by any number of methods, such as high-performance liquid chromatograph (HPLC), amino acid analysis, mass spectrometry, and the like.

#### *Salt Forms of Non-Naturally Occurring Melanocortin Analogs*

**[0332]** The non-naturally occurring melanocortin analog peptides of the present technology may be in the form of any salt. The term "pharmaceutically acceptable salts" refers to salts prepared from non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Exemplary salts are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine,

hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

**[0333]** When the peptides of the present technology are basic, acid addition salts may be prepared from non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, carboxylic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Acid addition salts of the peptides of the present technology are prepared in a suitable solvent from the peptide and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, citric, tartaric, maleic, succinic or methanesulfonic acid. The acetate salt form is especially useful. Where the peptides of the present technology include an acidic moiety, suitable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.

#### ***Weight Loss Agents***

**[0334]** The present technology comprises combination therapies including a non-naturally occurring melanocortin analog and a weight loss agent. In some embodiments, the non-naturally occurring melanocortin analog is a non-naturally occurring melanocortin agonist analog. The combination therapy may be useful in effecting weight loss in a subject in need thereof. The combination therapy may further be useful in effecting weight loss in a subject in need thereof while preserving lean mass, e.g., muscle and bone mass in the subject. For example, subjects who achieve weight loss using pharmaceutical combinations of the present technology may shed less lean mass, e.g., muscle and bone mass, than subjects who achieve weight loss using a weight loss agent alone. Additionally, or alternatively, subjects who achieve weight loss using pharmaceutical combinations of the present technology may shed more fat mass, e.g., visceral fat mass, than subjects who achieve weight loss using a weight loss agent alone.

**[0335]** Combination therapies in accordance with the present technology comprise a weight loss agent. In some embodiments, the weight loss agent is useful for treating and/or preventing metabolic dysfunction or one or more symptoms of metabolic dysfunction in a subject. The present technology is expected to be useful for subjects that may receive, have received, or are receiving one or more doses of a weight loss agent regardless of the underlying disease or condition that the subject has or develops.

**[0336]** Combination therapies of the present technology may include any conventional weight loss agent known in the art. Non-limiting examples of conventional weight loss agents include antihyperglycemic agents such as metformin, sulfonylureas (e.g., glimepiride, glipizide, and glyburide), meglitinides (e.g., repaglinide and nateglinide), thiazolidinediones (e.g., pioglitazone, rosiglitazone), dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, saxagliptin, and linagliptin), sodium-glucose cotransporter-2 (SGLT-2) inhibitors (e.g., empagliflozin, ertugliflozin, dapagliflozin, and canagliflozin), alpha-glucosidase inhibitors (e.g., acarbose and miglitol), bromocriptine, and colesevelam; glucagon-like peptide 1 (GLP-1) receptor agonists such as semaglutide (Ozempic®, Wegovy® and Rybelsus®), danuglipron, lotiglipron, orforglipron, exenatide (Byetta® and Bydureon®), liraglutide (Victoza® and Saxenda®), dulaglutide (Trulicity®), albiglutide (Tanzeum®), taspoglutide, and lixisenatide (Lyxumia® and Adlyxin®); glucose-dependent insulinotropic polypeptide (GIP) receptor agonists such as synthetic incretin hormone and long-acting GIP receptor agonists such as LY3537021; dual GLP-1/GIP receptor agonists such as tirzepatide (Mounjaro™ and Zepbound™); GLP-1/glucagon receptor coagonists such as efinopegdutide (MK-6024) and mazdutide; GLP-1/GIP/glucagon receptor trifunctional agonists such as retatrutide; amylin agonists such as amylin hormone analogue; neuregulin 4 (NRG4) agonists; peptide YY analog agonists; patatin-like phospholipase domain-containing protein 3 (PNPLA3) siRNA; lipase inhibitors such as orlistat (Xenical or Alli); norepinephrine and dopamine reuptake inhibitors such as bupropion-naltrexone (Contrave®); antiepileptics such as phentermine-topiramate (Qsymia®); and melanocortin 4 (MC4) receptor agonists such as setmelanotide (Imcivree®).

**[0337]** In some embodiments, the weight loss agent is in a free base form. In other embodiments, the weight loss agent is in a salt form. Any salt form of the weight loss agent

known in the art may be used in the methods of the present technology. For example, when the weight loss agent is a salt form of setmelanotide, it may be setmelanotide acetate.

**[0338]** In some embodiments, the pharmaceutical combination comprises one weight loss agent. In other embodiments, the pharmaceutical combination comprises two or more weight loss agents. In some embodiments in which the pharmaceutical combination comprises two or more weight loss agents, the two or more weight loss agents are from the same class of weight loss agents, e.g., the two or more weight loss agents are GLP-1 agonists. Alternatively, in some embodiments in which the pharmaceutical combination comprises two or more weight loss agents, each of the two or more weight loss agents are from a different class of weight loss agents, e.g., one weight loss agent is a GLP-1 agonist, another is a GIP agonist, and so on.

**[0339]** In some embodiments, the weight loss agent is selected from GLP-1 receptor agonists, GIP receptor agonists including long-acting GIP receptor agonists, a dual GLP-1/GIP receptor agonists, GLP-1/glucagon receptor coagonists, GLP-1/GIP/glucagon receptor trifunctional agonists, and melanocortin 4 (MC4) receptor agonists. In some embodiments, the weight loss agent is selected from GLP-1 receptor agonists, GIP receptor agonists, a dual GLP-1/GIP receptor agonists, GLP-1/glucagon receptor coagonists, and GLP-1/GIP/glucagon receptor trifunctional agonists.

**[0340]** In some embodiments, the weight loss agent is a GLP-1 receptor agonist. In some embodiments, the weight loss agent is a GLP-1 receptor agonist and is one or more of semaglutide (Ozempic® and Wegovy®), danuglipron, lotiglipron, orforglipron, exenatide (Byetta® an Bydureon®), liraglutide (Victoza® and Saxenda®), dulaglutide (Trulicity®), albiglutide (Tanzeum®), taspoglutide, and lixisenatide (Lyxumia®). In some embodiments, the GLP-1 receptor agonist is one or more of semaglutide (Ozempic®, Wegovy® and Rybelsus®), exenatide (Byetta® an Bydureon®), liraglutide (Victoza® and Saxenda®), dulaglutide (Trulicity®), albiglutide (Tanzeum®), and lixisenatide (Lyxumia® and Adlyxin®). In some embodiments, the GLP-1 receptor agonist is danuglipron. In some embodiments, the GLP-1 receptor agonist is lotiglipron. In some embodiments, the GLP-1 receptor agonist is orforglipron. In some embodiments, the GLP-1 receptor agonist is taspoglutide. In some embodiments, the GLP-1 receptor agonist is semaglutide (e.g., Ozempic® or Wegovy®). In

some embodiments, the GLP-1 receptor agonist is exenatide (Byetta® and Bydureon®). In some embodiments, the GLP-1 receptor agonist is liraglutide (Victoza® and Saxenda®). In some embodiments, the GLP-1 receptor agonist is dulaglutide (Trulicity®). In some embodiments, the GLP-1 receptor agonist is albiglutide (Tanzeum®). In some embodiments, the GLP-1 receptor agonist is lixisenatide (Lyxumia® and Adlyxin®).

**[0341]** Various other GLP-1 receptor agonists which may be employed as a weight loss agent in the present technology include, but are not limited to, peptides and compounds disclosed in WO2006/134340, WO2007/100535, WO2008/10101, WO2008/152403, WO2009/155257, WO2009/155258, WO2010/070252, WO2010/070253, WO2010/070255, WO2010/070251, WO2011/006497, WO2011/160630, WO2011/160633, WO2013/092703, WO2014/041195, WO2015/055802, WO2015/149627, WO2015/155139, WO2015/155140, WO2015/155141, WO2015/155151, WO2015/193378, WO2015/193381, WO2016/0154014, and WO2016/046753, which are incorporated herein by reference in their entireties.

**[0342]** In some embodiments, the weight loss agent is a GIP receptor agonist, such as a long-acting GIP receptor agonist. In some embodiments, the weight loss agent is LY3537021.

**[0343]** In other embodiments, the pharmaceutical combination comprises a first weight loss agent which is a long-acting GIP receptor agonist and a second weight loss agent which is a GLP-1 receptor agonist. The long-acting GIP receptor agonist may be LY3537021 and the GLP-1 receptor agonist may be any one of semaglutide (Ozempic® and Wegovy®), danuglipron, lotiglipron, orforglipron, exenatide (Byetta® and Bydureon®), liraglutide (Victoza® and Saxenda®), dulaglutide (Trulicity®), albiglutide (Tanzeum®), taspoglutide, and lixisenatide (Lyxumia®). In some embodiments, the GLP-1 receptor agonist is one or more of semaglutide (Ozempic®, Wegovy® and Rybelsus®), exenatide (Byetta® and Bydureon®), liraglutide (Victoza® and Saxenda®), dulaglutide (Trulicity®), albiglutide (Tanzeum®), and lixisenatide (Lyxumia® and Adlyxin®). In some embodiments, the first weight loss agent is LY3537021, and the second weight loss agent is liraglutide.

**[0344]** In some embodiments, the weight loss agent is a bifunctional or trifunctional GLP-1 agonist, e.g., a GLP-1 agonist that also has agonist activity at one or two other

receptors. In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist. In some embodiments, the weight loss agent is tirzepatide (Mounjaro™ and Zepbound™). In some embodiments, the weight loss agent is a dual GIP/GLP-1 receptor agonist disclosed in US 2023/0293638, the entirety of which is incorporated herein by reference in its entirety.

**[0345]** In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist. In some embodiments, the weight loss agent is efinopegdutide or mazdutide. In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist. In some embodiments, the weight loss agent is retatrutide.

**[0346]** In some embodiments, the weight loss agent is an MC4 receptor agonist. In some embodiments, the weight loss agent is setmelanotide (e.g., Imcivree®).

### ***Pharmaceutical Compositions, Formulations, and Administration***

#### ***Pharmaceutical Compositions***

##### ***Non-Naturally Occurring Melanocortin Analogs***

**[0347]** The non-naturally occurring melanocortin analogs of the present technology may be present in a pharmaceutical composition.

**[0348]** In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 10 mg/mL, relative to a total volume of the pharmaceutical composition.

**[0349]** In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some

embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, about 0.5 mg/mL to about 40 mg/mL, about 1 mg/mL to about 30 mg/mL, about 2.5 mg/mL to about 20 mg/mL, about 5 mg/mL to about 15 mg/mL, or about 5 mg/mL to about 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the pharmaceutical composition.

**[0350]** In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least 0.1 mg/mL to at least 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least 0.1 mg/mL to at least 50 mg/mL, at least 0.5 mg/mL to at least 40 mg/mL, at least 1 mg/mL to at least 30 mg/mL, at least 2.5 mg/mL to at least 20 mg/mL, at least 5 mg/mL to at least 15 mg/mL, or at least 5 mg/mL to at least 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least 10 mg/mL, relative to a total volume of the pharmaceutical composition.

**[0351]** In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least about 0.1 mg/mL to at least about 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least about 0.1 mg/mL to at least about 50 mg/mL, at least about 0.5 mg/mL to at least about 40 mg/mL, at least about 1 mg/mL to at least about 30 mg/mL, at least about 2.5 mg/mL to at least about 20 mg/mL, at least about 5 mg/mL to at least about 15 mg/mL, or at least about 5 mg/mL to at least about 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a

concentration of at least about 10 mg/mL, relative to a total volume of the pharmaceutical composition.

Weight Loss Agents & Combination Therapies

**[0352]** Combination therapies of the present technology may comprise the non-naturally occurring melanocortin analog and the weight loss agent as distinct compositions. For example, the weight loss agent may be present in a first pharmaceutical composition and the non-naturally occurring analog may be present in a second pharmaceutical composition. As will be described in more detail below, the first and second pharmaceutical compositions may be administered concurrently, sequentially, or cyclically. Alternatively, pharmaceutical combinations of the present technology may be formulated as a single pharmaceutical composition comprising a non-naturally occurring melanocortin analog and a weight loss agent.

**[0353]** In some embodiments of the combination therapy, the weight loss agent is present in a first pharmaceutical composition and the non-naturally occurring melanocortin analog is present in a second pharmaceutical composition. The weight loss agent may be formulated with one or more pharmaceutically acceptable carriers and/or excipients to form the first pharmaceutical composition. Similarly, the non-naturally occurring melanocortin analog may be formulated with one or more pharmaceutically acceptable carriers and/or excipients to form the second pharmaceutical composition. In some embodiments, the first and the second pharmaceutical compositions are different.

**[0354]** In some embodiments, the first pharmaceutical composition comprising the weight loss agent and the second pharmaceutical composition comprising the non-naturally occurring melanocortin analog are administered concurrently.

**[0355]** In other embodiments, the first pharmaceutical composition and the second pharmaceutical composition are administered sequentially. In sequential administration, the first pharmaceutical composition may be administered before the second pharmaceutical composition, after the second pharmaceutical composition, or both. Likewise, the second pharmaceutical composition may be administered before the first pharmaceutical composition, after the first pharmaceutical composition, or both.



**[0356]** In still other embodiments, the first pharmaceutical composition and the second pharmaceutical composition may be administered cyclically.

**[0357]** In some embodiments, the weight loss agent is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, the weight loss agent is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.005 mg/mL to 750 mg/mL, 0.01 mg/mL to 500 mg/mL, 0.05 mg/mL to 250 mg/mL, 0.1 mg/mL to 100 mg/mL, 0.2 mg/mL to 80 mg/mL, 0.3 mg/mL to 60 mg/mL, 0.4 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 0.5 mg/mL to 30 mg/mL, or 1 mg/mL to 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0358]** In some embodiments, the weight loss agent is a GLP-1 receptor agonist and is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, the GLP-1 receptor agonist is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.005 mg/mL to 750 mg/mL, 0.01 mg/mL to 500 mg/mL, 0.05 mg/mL to 250 mg/mL, 0.08 mg/mL to 50 mg/mL, 0.1 mg/mL to 50 mg/mL, 0.2 mg/mL to 10 mg/mL, 0.3 mg/mL to 8 mg/mL, 0.5 mg/mL to 5 mg/mL, or 1 mg/mL to 3.5 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0359]** In some embodiments, the weight loss agent is semaglutide and is present in the first pharmaceutical composition in a concentration of 0.5 mg/mL to 5.0 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, semaglutide is present in the first pharmaceutical composition in a concentration of 0.5 mg/mL to 5.0 mg/mL, 0.5 mg/mL to 4.0 mg/mL, 0.6 mg/mL to 3.5 mg/mL, 0.65 mg/mL to 3.2 mg/mL, 0.65 mg/mL to 3.0 mg/mL, 0.8 mg/mL to 2.8 mg/mL, 1.0 mg/mL to 3.0 mg/mL, 1.0 mg/mL to 2.8 mg/mL, 1.2 mg/mL to 3.0 mg/mL, 1.2 mg/mL to 2.8 mg/mL, 0.6 mg/mL to 2.3 mg/mL, 0.6 mg/mL to 2.0 mg/mL, 0.6 mg/mL to 1.8 mg/mL, 0.6 mg/mL to 1.5 mg/mL, or 1.3 mg/mL to 2.8 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, semaglutide is present in the first pharmaceutical composition in a concentration of about 0.68 mg/mL, 1 mg/mL, 1.34 mg/mL, 2.0 mg/mL, 2.26 mg/mL, 2.68 mg/mL, or 3.2 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0360]** In some embodiments, the weight loss agent is Ozempic®. In some embodiments, the weight loss agent is Wegovy®.

**[0361]** In some embodiments, the weight loss agent is semaglutide and is present in the first pharmaceutical composition in an amount of about 0.5 mg to about 40 mg. In some embodiments, semaglutide is present in the first pharmaceutical composition in an amount of 0.5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg. In some embodiments, semaglutide is present in the first pharmaceutical composition in an amount of about 3 mg or less, 7 mg or less, or 14 mg or less.

**[0362]** In some embodiments, the weight loss agent is Rybelsus®.

**[0363]** In some embodiments, the weight loss agent is exenatide and is present in the first pharmaceutical composition in a concentration of 5 µg/mL to 1000 µg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, exenatide is present in the first pharmaceutical composition in a concentration of 5 µg/mL to 1000 µg/mL, 10 µg/mL to 900 µg/mL, 20 µg/mL to 800 µg/mL, 50 µg/mL to 700 µg/mL, 70 µg/mL to 600 µg/mL, 90 µg/mL to 550 µg/mL, 100 µg/mL to 500 µg/mL, 110 µg/mL to 450 µg/mL, 120 µg/mL to 400 µg/mL, 130 µg/mL to 350 µg/mL, 140 µg/mL to 350 µg/mL, 150 µg/mL to 300 µg/mL, 200 µg/mL to 300 µg/mL, or 200 µg/mL to 250 µg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, exenatide is present in the first pharmaceutical composition in a concentration of about 250 µg/mL, relative to a total volume of the first pharmaceutical composition.

**[0364]** In some embodiments, the weight loss agent is Byetta®.

**[0365]** In some embodiments, the weight loss agent is exenatide and is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 5.0 mg/mL, 0.25 mg/mL to 4.5 mg/mL, 0.5 mg/mL to 4.5 mg/mL, 0.75 mg/mL to 4.0 mg/mL, 1.0 mg/mL to 3.75 mg/mL, 1.25 mg/mL to 3.5 mg/mL, 1.5 mg/mL to 3.25 mg/mL, 1.75 mg/mL to 3.0 mg/mL, 2.0 mg/mL to 2.75 mg/mL, or 2.25 mg/mL to 2.5 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, exenatide is present in the first

pharmaceutical composition in a concentration of about 2.35 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0366]** In some embodiments, the weight loss agent is Bydureon®.

**[0367]** In some embodiments, the weight loss agent is dulaglutide and is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 100 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, dulaglutide is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 100 mg/mL, 0.05 mg/mL to 90 mg/mL, 0.1 mg/mL to 80 mg/mL, 0.2 mg/mL to 70 mg/mL, 0.3 mg/mL to 60 mg/mL, 0.5 mg/mL to 50 mg/mL, 0.6 mg/mL to 45 mg/mL, 0.7 mg/mL to 40 mg/mL, 0.8 mg/mL to 35 mg/mL, 0.9 mg/mL to 30 mg/mL, 1.0 mg/mL to 25 mg/mL, 1.1 mg/mL to 20 mg/mL, 1.2 mg/mL to 15 mg/mL, or 1.5 mg/mL to 10 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, dulaglutide is present in the first pharmaceutical composition in a concentration of about 1.5 mg/mL, 3.0 mg/mL, 6.0 mg/mL, or 9.0 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0368]** In some embodiments, the weight loss agent is Trulicity®.

**[0369]** In some embodiments, the weight loss agent is orforglipron and is present in the first pharmaceutical composition in an amount of about 0.01 mg to about 100 mg. In some embodiments, orforglipron is present in the first pharmaceutical composition in an amount of 0.01 mg to 100 mg, 0.05 mg to 90 mg, 0.1 mg to 80 mg, 0.2 mg to 70 mg, 0.3 mg to 60 mg, 0.4 mg to 50 mg, 0.5 mg to 45 mg, 0.6 mg to 40 mg, 0.7 mg to 35 mg, 0.8 mg to 30 mg, 0.9 mg to 25 mg, 1.0 mg to 20 mg, 1.1 mg to 18 mg, 1.2 mg to 16 mg, 1.3 mg to 14 mg, 1.4 mg to 12 mg, or 1.5 mg to 10 mg. In some embodiments, orforglipron is present in the first pharmaceutical composition in an amount of about 2 mg or less, 4 mg or less, 5 mg or less, 6 mg or less, 8 mg or less, 12 mg or less, 16 mg or less, or 24 mg or less.

**[0370]** In some embodiments, the weight loss agent is a long-acting GIP receptor agonist and is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, the long-acting GIP receptor agonist is present in the first

pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.01 mg/mL to 750 mg/mL, 0.05 mg/mL to 500 mg/mL, 0.1 mg/mL to 250 mg/mL, 0.5 mg/mL to 100 mg/mL, 1 mg/mL to 90 mg/mL, 1.5 mg/mL to 80 mg/mL, 2 mg/mL to 70 mg/mL, 2.5 mg/mL to 60 mg/mL, 3 mg/mL to 50 mg/mL, 3.5 mg/mL to 45 mg/mL, 4 mg/mL to 40 mg/mL, 4.5 mg/mL to 35 mg/mL, or 5 mg/mL to 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0371]** In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist and is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, the dual GLP-1/GIP receptor agonist is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.01 mg/mL to 750 mg/mL, 0.05 mg/mL to 500 mg/mL, 0.1 mg/mL to 250 mg/mL, 0.5 mg/mL to 100 mg/mL, 1 mg/mL to 90 mg/mL, 1.5 mg/mL to 80 mg/mL, 2 mg/mL to 70 mg/mL, 2.5 mg/mL to 60 mg/mL, 3 mg/mL to 50 mg/mL, 3.5 mg/mL to 45 mg/mL, 4.0 mg/mL to 40 mg/mL, 4.5 mg/mL to 35 mg/mL, or 5 mg/mL to 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0372]** In some embodiments, the weight loss agent is tirzepatide and is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, tirzepatide is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.01 mg/mL to 750 mg/mL, 0.05 mg/mL to 500 mg/mL, 0.1 mg/mL to 250 mg/mL, 0.5 mg/mL to 100 mg/mL, 1 mg/mL to 90 mg/mL, 1.5 mg/mL to 80 mg/mL, 2 mg/mL to 70 mg/mL, 2.5 mg/mL to 60 mg/mL, 3 mg/mL to 50 mg/mL, 3.5 mg/mL to 45 mg/mL, 4.0 mg/mL to 40 mg/mL, 4.5 mg/mL to 35 mg/mL, or 5 mg/mL to 30 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, tirzepatide is present in the first pharmaceutical composition in a concentration of about 5 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, or 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0373]** In some embodiments, the weight loss agent is Mounjaro™. In some embodiments, the weight loss agent is Zepbound™.

**[0374]** In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is present in the first pharmaceutical composition in an amount of about 0.5 mg to about 50 mg. In some embodiments, the GLP-1/glucagon receptor coagonist is present in the first pharmaceutical composition in an amount of 0.5 mg to 50 mg, 1 mg to 50 mg, 5 mg to 50 mg, 0.5 mg to 40 mg, 1 mg to 40 mg, 5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 5 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2 mg to 20 mg, 5 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg.

**[0375]** In some embodiments, the weight loss agent is mazdutide and is present in the first pharmaceutical composition in an amount of about 0.5 mg to about 50 mg. In some embodiments, mazdutide is present in the first pharmaceutical composition in an amount of 0.5 mg to 50 mg, 1 mg to 50 mg, 5 mg to 50 mg, 0.5 mg to 40 mg, 1 mg to 40 mg, 5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 5 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2 mg to 20 mg, 5 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg. In some embodiments, mazdutide is present in the first pharmaceutical composition in an amount of about 5 mg or less, 6 mg or less, 7 mg or less, 8 mg or less, 9 mg or less, or 10 mg or less.

**[0376]** In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist and is present in the first pharmaceutical composition in an amount of about 0.5 mg to about 50 mg. In some embodiments, the GLP-1/GIP/glucagon receptor trifunctional agonist is present in the first pharmaceutical composition in an amount of 0.5 mg to 50 mg, 1 mg to 50 mg, 5 mg to 50 mg, 0.5 mg to 40 mg, 1 mg to 40 mg, 5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 5 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2 mg to 20 mg, 5 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg.

**[0377]** In some embodiments, the weight loss agent is retatrutide and is present in the first pharmaceutical composition in an amount of about 0.5 mg to about 50 mg. In some embodiments, retatrutide is present in the first pharmaceutical composition in an amount of 0.5 mg to 50 mg, 1 mg to 50 mg, 5 mg to 50 mg, 0.5 mg to 40 mg, 1 mg to 40 mg, 5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 5 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2

mg to 20 mg, 5 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg. In some embodiments, retatrutide is present in the first pharmaceutical composition in an amount of about 0.5 mg or less, 1.5 mg or less, 3 mg or less, 6 mg or less, 9 mg or less, or 12 mg or less.

**[0378]** In some embodiments, the weight loss agent is an MC4 receptor agonist and is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, the MC4 receptor agonist is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.01 mg/mL to 900 mg/mL, 0.05 mg/mL to 800 mg/mL, 0.1 mg/mL to 700 mg/mL, 0.5 mg/mL to 600 mg/mL, 1 mg/mL to 500 mg/mL, 2.5 mg/mL to 400 mg/mL, 5 mg/mL to 300 mg/mL, 7.5 mg/mL to 200 mg/mL, 10 mg/mL to 100 mg/mL, 25 mg/mL to 90 mg/mL, or 50 mg/mL to 75 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0379]** In some embodiments, the weight loss agent is setmelanotide, and setmelanotide is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, setmelanotide is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.005 mg/mL to 500 mg/mL, 0.01 mg/mL to 250 mg/mL, 0.05 mg/mL to 100 mg/mL, 0.1 mg/mL to 80 mg/mL, 0.5 mg/mL to 60 mg/mL, 1 mg/mL to 50 mg/mL, 2 mg/mL to 40 mg/mL, 2.5 mg/mL to 35 mg/mL, 3 mg/mL to 30 mg/mL, 3.5 mg/mL to 25 mg/mL, 4 mg/mL to 20 mg/mL, 4.5 mg/mL to 20 mg/mL, or 5 mg/mL to 15 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, setmelanotide is present in the first pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[0380]** In some embodiments, the weight loss agent lmcivree®.

**[0381]** In some embodiments, the first pharmaceutical composition comprising the weight loss agent formulated for intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, or oral administration. In some embodiments, the

first pharmaceutical composition comprising the weight loss agent is formulated for subcutaneous administration. Alternatively, in some embodiments, the first pharmaceutical composition comprising the weight loss agent is formulated for oral administration.

**[0382]** The first pharmaceutical composition may comprise one or more pharmaceutically acceptable carriers and/or excipients such as, for example, buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, and antioxidants. For example, when the first pharmaceutical composition is formulated for subcutaneous administration, the one or more pharmaceutically acceptable carriers and/or excipients may comprise water. In such embodiments, the first pharmaceutical composition contains 0.1 to 99.9999 wt.%, 1 to 99.999 wt.%, 5 to 99.99 wt.%, 10 to 99.9 wt.%, 15 to 99 wt.%, 20 to 90 wt.%, 30 to 85 wt.%, 40 to 80 wt.%, 50 to 75 wt.%, or 60 to 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the first pharmaceutical composition.

**[0383]** In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 10 mg/mL, relative to a total volume of the second pharmaceutical composition.

**[0384]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5

mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the second pharmaceutical composition.

**[0385]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the second pharmaceutical composition.

**[0386]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the second pharmaceutical composition.



**[0387]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the second pharmaceutical composition.

**[0388]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the second pharmaceutical composition.

**[0389]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the

second pharmaceutical composition. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the second pharmaceutical composition.

**[0390]**

*Formulations*

**[0391]** The pharmaceutical composition comprising the non-naturally occurring melanocortin analog may be formulated for intraperitoneal, intravenous, parenteral, depot, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration. In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for subcutaneous administration. In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for oral administration. In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for depot administration. In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is present in a single composition with the weight loss agent. In some embodiments, the non-naturally occurring melanocortin analog and the weight loss agent are present in different pharmaceutical compositions (e.g., a first pharmaceutical composition and a second pharmaceutical composition) are formulated for the same route of administration or are formulated for different routes of administration.

**[0392]** In some embodiments, the pharmaceutical composition further comprises a pharmaceutical salt. Any pharmaceutical salt known in the art may be included in the pharmaceutical composition.

**[0393]** Pharmaceutical compositions comprising the non-naturally occurring melanocortin analog may be administered using any means known in the art, including orally, rectally, vaginally, ocularly, intranasally, topically, parenterally, or by injection. If administered by injection, the injection may be intravenous (IV), subcutaneous (SC), intramuscular (IM), intraperitoneal (IP), intracerebroventricular (ICV), or other means known in the art. Compositions administered by injection may be formulated for depot injection.

Pharmaceutical compositions may be formulated by any means known in the art, including but not limited to formulation as tablets, capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, pessaries, ocular drops, skin patches, orally soluble formulations, enteric formulations, solutions sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, antioxidants and other agents known in the art. In general, any route of administration by which the compositions are introduced across an epidermal layer of cells may be employed. Administration includes topical delivery. Administration includes delivery across the epithelium. Administration includes delivery through the gastrointestinal tract. Administration includes delivery across the blood brain barrier. Administration includes delivery through mucous membranes, buccal administration, ophthalmic administration, oral administration, dermal administration, inhalation administration, nasal administration, urethral administration, vaginal administration, rectal administration, and the like.

**[0394]** In order to facilitate delivery of the active ingredients, to enhance dispersion, solubility, and stability of the active ingredients, and/or to reduce adverse injection site reactions, the pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers and/or excipients.

**[0395]** The pharmaceutical composition may comprise one or more pharmaceutically acceptable carriers and/or excipients such as, for example, buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, and antioxidants. For example, when the first pharmaceutical composition is formulated for subcutaneous administration, the one or more pharmaceutically acceptable carriers and/or excipients may comprise water.

**[0396]** In some embodiments, the first pharmaceutical composition contains 0.1 to 99.9999 wt.%, 1 to 99.999 wt.%, 5 to 99.99 wt.%, 10 to 99.9 wt.%, 15 to 99 wt.%, 20 to 90 wt.%, 30 to 85 wt.%, 40 to 80 wt.%, 50 to 75 wt.%, or 60 to 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the first pharmaceutical composition.

**[0397]** In some embodiments, the first pharmaceutical composition contains 0.1 to 99.9999 wt.%, 1 to 99.999 wt.%, 5 to 99.99 wt.%, 10 to 99.9 wt.%, 15 to 99 wt.%, 20 to 90 wt.%, 30 to 85 wt.%, 40 to 80 wt.%, 50 to 75 wt.%, or 60 to 70 wt.% of the one or more

pharmaceutically acceptable carriers and/or excipients relative to a total weight of the first pharmaceutical composition.

**[0398]** In some embodiments, the first pharmaceutical composition contains at least 0.1 to at least 99.9999 wt.%, at least 1 to at least 99.999 wt.%, at least 5 to at least 99.99 wt.%, at least 10 to at least 99.9 wt.%, at least 15 to at least 99 wt.%, at least 20 to at least 90 wt.%, at least 30 to at least 85 wt.%, at least 40 to at least 80 wt.%, at least 50 to at least 75 wt.%, or at least 60 to at least 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the first pharmaceutical composition.

**[0399]** In some embodiments, the first pharmaceutical composition contains at least about 0.1 to at least about 99.9999 wt.%, at least about 1 to at least about 99.999 wt.%, at least about 5 to at least about 99.99 wt.%, at least about 10 to at least about 99.9 wt.%, at least about 15 to at least about 99 wt.%, at least about 20 to at least about 90 wt.%, at least about 30 to at least about 85 wt.%, at least about 40 to at least about 80 wt.%, at least about 50 to at least about 75 wt.%, or at least about 60 to at least about 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the first pharmaceutical composition.

**[0400]** Any pharmaceutically acceptable carriers and/or excipients known in the art may be included in the pharmaceutical composition. Non-limiting examples of pharmaceutically acceptable carriers and/or excipients include buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, preservatives, lipids, and antioxidants. The pharmaceutical composition may comprise any combination of the one or more pharmaceutically acceptable carriers and/or excipients previously described in relation to the first and pharmaceutical compositions. In some embodiments, the one or more pharmaceutically acceptable carriers and/or excipients comprise water.

**[0401]** To facilitate delivery of the non-naturally occurring melanocortin analog, the pharmaceutical composition may comprise one or more pharmaceutically acceptable carriers and/or excipients. Other pharmaceutically acceptable carriers and/or excipients may be included in the pharmaceutical composition to enhance dispersion, solubility, and stability of the non-naturally occurring melanocortin analog, and to reduce adverse injection site reactions.

**[0402]** In some embodiments, the one or more pharmaceutically acceptable carriers and/or excipients are isotonic.

**[0403]** In some embodiments, the salt is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, about 1 mg/mL to about 25 mg/mL, or about 5 mg/mL to about 10 mg/mL, relative to a total volume of the composition.

**[0404]** In some embodiments, the salt is present in the pharmaceutical composition in a concentration of at least 0.1 mg/mL to at least 50 mg/mL, at least 1 mg/mL to at least 25 mg/mL, or at least 5 mg/mL to at least 10 mg/mL, relative to a total volume of the composition.

**[0405]** In order to achieve a desirable tonicity, the pharmaceutical composition may further include a salt such as sodium chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride.

**[0406]** In some embodiments, the salt is present in the pharmaceutical composition in a concentration of at least about 0.1 mg/mL to at least about 50 mg/mL, at least about 1 mg/mL to at least about 25 mg/mL, or at least about 5 mg/mL to at least about 10 mg/mL, relative to a total volume of the composition.

**[0407]** Pharmaceutically acceptable carriers and/or excipients that may be included in the pharmaceutical composition generally include a pH buffered aqueous solution comprising one or more of the following components: (a) sodium acetate, (b) Tris, and (c) water. In some embodiments, all components are compatible with the non-naturally occurring melanocortin analog (i.e., do not react or cause the non-naturally occurring melanocortin analog to react) and are homogeneously dispersed or dissolved uniformly in the composition.

**[0408]** In the pH buffered solution of the pharmaceutical composition, the water may act as a diluent and include, without limitation, water for injection (WFI), sterile water, bacteriostatic water for injection (BWFI), distilled water, bidistilled water, deionized water, deionized distilled water, and reverse osmosis water. In some embodiments, the water present in the pH buffered aqueous solution is water for injection.

**[0409]** In some embodiments, the pharmaceutical composition includes water in an amount of about 1 wt% to about 90 wt%, about 10 wt% to about 75 wt%, or about 25 wt% to about 50 wt%, relative to a total weight of the composition.

**[0410]** In some embodiments, the pharmaceutical composition includes water in an amount of at least 1 wt% to at least 90 wt%, at least 10 wt% to at least 75 wt%, or at least 25 wt% to at least 50 wt%, relative to a total weight of the composition.

**[0411]** In some embodiments, the pharmaceutical composition includes water in an amount of at least about 1 wt% to at least about 90 wt%, at least about 10 wt% to at least about 75 wt%, or at least about 25 wt% to at least about 50 wt%, relative to a total weight of the composition. In some embodiments, sodium acetate is present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

**[0412]** In some embodiments, sodium acetate is present in the pharmaceutical composition in a concentration of about 6 mg/mL to about 8 mg/mL, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical composition in a concentration of 6 mg/mL, 6.5 mg/mL, 7 mg/mL, 7.1 mg/mL, 7.5 mg/mL, or 8 mg/mL, relative to a total volume of the composition.

**[0413]** In some embodiments, sodium acetate is present in the pharmaceutical composition in a molar concentration of 5 mM to 700 mM, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical composition in a molar concentration of 5 mM to 700 mM, 10 mM to 600 mM, 20 mM to 500 mM, 30 mM to 400 mM, 40 mM to 300 mM, 50 mM to 200 mM, 60 mM to 100 mM, or 70 mM to 80 mM, relative to a total volume of the composition.

**[0414]** In some embodiments, sodium acetate is present in the pharmaceutical composition in a molar concentration of about 80 mM to about 100 mM, relative to a total volume of the composition. For example, sodium acetate may be present in the

pharmaceutical composition in a molar concentration of 80 mM, 85 mM, 87 mM, 90 mM, 95 mM, or 100 mM, relative to a total volume of the composition.

**[0415]** The term “Tris” refers to tris(hydroxymethyl)aminomethane, which is also known as Tris buffer, Tris base, TRIS, tromethamine, tromethamine buffer, Trizma®, Trisamine, Trometamol, Tromethane, Trisaminol, or THAM. In some embodiments, Tris is present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

**[0416]** In some embodiments, Tris is present in the pharmaceutical composition in a concentration of about 6 mg/mL to about 8 mg/mL, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a concentration of 6 mg/mL, 6.5 mg/mL, 7 mg/mL, 7.3 mg/mL, 7.6 mg/mL, or 8 mg/mL, relative to a total volume of the composition.

**[0417]** In some embodiments, Tris is present in the pharmaceutical composition in a molar concentration of 2 mM to 500 mM, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a molar concentration of 2 mM to 500 mM, 5 mM to 400 mM, 10 mM to 300 mM, 20 mM to 200 mM, 30 mM to 150 mM, 40 mM to 100 mM, 50 mM to 80 mM, or 60 mM to 70 mM, relative to a total volume of the composition.

**[0418]** In some embodiments, Tris is present in the pharmaceutical composition in a molar concentration of about 50 mM to about 70 mM, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a molar concentration of 50 mM, 55 mM, 60 mM, 65 mM, or 70 mM, relative to a total volume of the composition.

**[0419]** In some embodiments, the pH buffered aqueous solution provides the pharmaceutical composition with a pH equivalent or close to the physiological pH levels. This may reduce adverse injection site reactions and also provide the non-naturally

occurring melanocortin analog with enhanced stability and resistance to aggregation and degradation.

**[0420]** In some embodiments, a weight ratio of sodium acetate to Tris is about 1:4 to about 4:1, about 2:7 to about 7:2, about 1:3 to about 3:1, about 2:5 to about 5:2, about 1:2 to about 2:1, about 2:3 to about 3:2, or about 1:1. In some embodiments, the weight ratio of sodium acetate to Tris is about 1:1.

**[0421]** In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is about 1:1 to about 20:1, about 3:2 to about 15:1, about 2:1 to about 12:1, about 3:1 to about 10:1, about 4:1 to about 9:1, about 5:1 to about 8:1, or about 6:1 to about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is about 7:1.

**[0422]** In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to Tris is about 1:1 to about 20:1, about 3:2 to about 15:1, about 2:1 to about 12:1, about 3:1 to about 10:1, about 4:1 to about 9:1, about 5:1 to about 8:1, or about 6:1 to about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to Tris is about 7:1.

**[0423]** In addition to sodium acetate and Tris, the pharmaceutical composition may include other buffering agents. Non-limiting examples of additional buffering agents include saline, phosphate, phosphoric acid, citrate, succinate, gluconate, histidine, acetic acid, ascorbate, tartaric acid, maleic acid, glycine, lactate, lactic acid, ascorbic acid, imidazole, bicarbonate, carbonic acid, succinic acid, sodium benzoate, benzoic acid, gluconate, edetate, malate, imidazole, and mixtures thereof. In some embodiments, the pharmaceutical composition comprises acetic acid as an additional buffering agent.

**[0424]** The pharmaceutical composition may further comprise one or more chelating agents. Suitable chelating agents include, but are not limited to edetate disodium dihydrate, calcium disodium edetate, sodium edetate, calcium versetamide sodium, calteridol, and diethylenetriaminepentaacetic acid. In some embodiments, the pharmaceutical composition further comprises edetate disodium dihydrate.



**[0425]** The pharmaceutical composition may further comprise a preservative agent. Exemplary preservative agents include, but are not limited to, ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, phenol, m-cresol, benzyl alcohol, alpha-tocopherol, citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, benzalkonium chloride, phenoxyethanol, and methyl paraben. In some embodiments, when the pharmaceutical composition comprises a preservative agent, the preservative agent is phenol, benzyl alcohol, or a combination thereof.

**[0426]** If present in the pharmaceutical composition, the concentration of the preservative agent may range from 0.001 mg/mL to 50 mg/mL, 0.01 mg/mL to 25 mg/mL, 0.1 mg/mL to 10 mg/mL, or 1 mg/mL to 5 mg/mL, relative to a total volume of the composition.

**[0427]** The pharmaceutical composition may further comprise an emulsifier. Non-limiting examples of emulsifiers that may be included in the pharmaceutical composition include sodium carboxymethylcellulose, cetyl alcohol, glycerol monostearate, methylcellulose, and stearic acid. In some embodiments, when the pharmaceutical composition comprises an emulsifier, the emulsifier is sodium carboxymethylcellulose.

**[0428]** The pharmaceutical composition may further comprise a lipid. Lipids may enhance solubility and/or improve permeability of the non-naturally occurring melanocortin analog. In some embodiments, the lipid is a phospholipid. Non-limiting examples of phospholipids that may be included in the pharmaceutical composition include egg phosphatidylcholine, hydrogenated soybean phosphatidylcholine, glycerophosphocholine, lecithin, and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt. In some embodiments, when the pharmaceutical composition comprises a lipid, the lipid is N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt.

**[0429]** The pharmaceutical composition may further comprise a bulking agent. Inclusion of a bulking agent may increase the stability of the pharmaceutical composition. Non-limiting examples of bulking agents that may be included in the pharmaceutical

composition include sucrose, lactose, trehalose, mannitol, sorbitol, glucose, raffinose, glycine, histidine, and polyvinyl pyrrolidone. In some embodiments, when the pharmaceutical composition comprises a bulking agent, the bulking agent is mannitol.

**[0430]** In some embodiments, the pharmaceutical composition is in the form of an aqueous solution or a suspension. In some embodiments, the pharmaceutical composition is in the form of an emulsion. In some embodiments, the pharmaceutical composition is in the form of an aqueous solution. In some embodiments, the pharmaceutical composition is in the form of an aqueous solution which is clear, colorless, and/or free of visible foreign matter.

**[0431]** In some embodiments, the pharmaceutical composition has a pH ranging from about 6.5 to about 8.5. In some embodiments, the pharmaceutical composition has a pH of about 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, or 8.5.

**[0432]** In some embodiments, the pharmaceutical composition is basic and has a pH of about 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, or 8.5. In some embodiments, the pharmaceutical composition has a pH ranging from about 7.3 to about 7.4. In some embodiments, the pharmaceutical composition has a pH of 7.3 or 7.4.

**[0433]** In some embodiments, the pharmaceutical composition has an osmolality ranging from 250 mOsm/kg to 350 mOsm/kg. For example, the pharmaceutical composition may have an osmolality ranging from 250 mOsm/kg to 360 mOsm/kg, 260 mOsm/kg to 340 mOsm/kg, 270 mOsm/kg to 330 mOsm/kg, 280 mOsm/kg to 320 mOsm/kg, 290 mOsm/kg to 310 mOsm/kg, or about 300 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality of about 250 mOsm/kg, about 260 mOsm/kg, about 270 mOsm/kg, about 280 mOsm/kg, about 290 mOsm/kg, about 300 mOsm/kg, about 310 mOsm/kg, about 320 mOsm/kg, about 330 mOsm/kg, about 340 mOsm/kg, about 350 mOsm/kg, or about 360 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality ranging from about 275 mOsm/kg to about 330 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality of about 279 mOsm/kg, about 314 mOsm/kg, or about 329 mOsm/kg.

**[0434]** In some embodiments, the pharmaceutical composition has a viscosity ranging from about 0.5 cP to about 5 cP. For example, the pharmaceutical composition may have a viscosity ranging from about 0.5 cP to about 5 cP, about 0.75 cP to about 4.5 cP, about 1.0 cP to about 4 cP, about 1.2 cP to about 3.5 cP, about 1.3 cP to about 3 cP, about 1.4 cP to about 2.5 cP, about 1.5 cP to about 2 cP, or about 1.6 cP to about 1.8 cP. In some embodiments, the pharmaceutical composition has a viscosity of about 0.5 cP, 0.6 cP, 0.7 cP, 0.8 cP, 0.9 cP, 1.0 cP, 1.1 cP, 1.2 cP, 1.3 cP, 1.4 cP, 1.5 cP, 1.6 cP, 1.7 cP, 1.8 cP, 1.9 cP, or 2.0 cP. In some embodiments, the pharmaceutical composition has a viscosity of about 1.4 cP or about 1.6 cP.

**[0435]** In some embodiments, the pharmaceutical composition disclosed is formulated for parenteral administration, such as, for example, in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. The term “parenteral,” as used herein, includes subcutaneous, intravenous, intraperitoneal, intramuscular, and intralesional, or infusion techniques.

**[0436]** When the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration), the active ingredient(s) (e.g., the non-naturally occurring melanocortin analog) may be dissolved or suspended in the aforementioned carrier and/or excipient. Additional aqueous or non-aqueous carriers that may facilitate dissolution of the active ingredient include, but are not limited to, ethanol, benzyl alcohol, DMSO, polyethylene glycol, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, and/or various buffers.

**[0437]** In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises a non-naturally occurring melanocortin analog in a concentration of about 0.001 nmol, 0.005 nmol, 0.01 nmol, 0.02 nmol, 0.05 nmol, 0.1 nmol, 0.25 nmol, 0.5 nmol, 1 nmol, 2.5 nmol, 5 nmol, 10 nmol, 20 nmol, 25 nmol, 50 nmol, 100 nmol, 250 nmol, 500 nmol, or 1000 nmol, or even more, depending on the specific peptide selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

**[0438]** In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises sodium acetate

in a concentration of about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 76 mM, 77 mM, 78 mM, 79 mM, 80 mM, 81 mM, 82 mM, 83 mM, 84 mM, 85 mM, 86 mM, 87 mM, 88 mM, 89 mM, 90 mM, 91 mM, 92 mM, 93 mM, 94 mM, 95 mM, 96 mM, 97 mM, 98 mM, 99 mM, 100 mM, 105 mM, 110 mM, 120 mM, 130 mM, 140 mM, 150 mM, 160 mM, 170 mM, 180 mM, 190 mM, or 200 mM.

**[0439]** In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises Tris in a concentration of about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, 90 mM, 95 mM, 100 mM, 105 mM, 110 mM, or 120 mM.

**[0440]** Alternatively, in some embodiments, the pharmaceutical composition is formulated for intranasal administration. When the pharmaceutical composition is formulated for intranasal administration, the composition may comprise one or more pharmaceutically acceptable carriers and/or excipients to facilitate delivery and enhance dispersion, solubility, and stability of the non-naturally occurring melanocortin analog.

**[0441]** The pharmaceutical composition may be formulated to be delivered by nose drop, spray device, or topical solution. In some embodiments, the pharmaceutical composition may be formulated as an aerosol, atomizer, inhalation, insufflation, metered-dose inhaler, or nebulizer. In some embodiments, the composition includes a propellant, such as hydrofluoroalkane.

**[0442]** When the pharmaceutical composition is formulated for intranasal administration, the active ingredient(s) (e.g., the non-naturally occurring melanocortin analog) may be dissolved or suspended in the one or more pharmaceutically acceptable carriers and/or excipients. Additional aqueous or non-aqueous carriers that may facilitate dissolution of the active ingredient include, but are not limited to, ethanol, benzyl alcohol, DMSO, polyethylene glycol, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, and/or various buffers.

**[0443]** In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises the non-naturally occurring melanocortin analog in a concentration of about 0.001 nmol, 0.005 nmol, 0.01 nmol, 0.02 nmol, 0.05 nmol, 0.1 nmol, 0.25 nmol, 0.5 nmol, 1 nmol, 2.5 nmol, 5 nmol, 10 nmol, 20 nmol, 25 nmol, 50 nmol, 100 nmol, 250 nmol, 500 nmol, or 1000 nmol, or even more, depending on the specific peptide selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

**[0444]** In some embodiments, the pharmaceutical composition is formulated for intranasal administration and is configured to be administered using a spray device or nasal inhaler. The spray device or nasal inhaler may be configured to deliver about 1mg to about 100mg per spray. In some embodiments, the spray device or nasal inhaler is configured to deliver 1mg to 100mg, 5mg to 90mg, 10mg to 80mg, 15mg to 70mg, 20mg to 60mg, 25mg, to 50mg, or 30mg to 40mg per spray.

**[0445]** In some embodiments, the pharmaceutical composition is formulated for intranasal administration and has a pH approximating the normal pH range of the nasal fluid. Accordingly, in some embodiments, the pharmaceutical composition has a pH ranging from about 5.5 to about 6.5. In some embodiments, the pharmaceutical composition has a pH of about 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, or 6.5.

**[0446]** Pharmaceutically acceptable carriers and/or excipients that may be included in the pharmaceutical composition formulated for intranasal administration may generally include (i) one or more antioxidants, (ii) one or more preservatives, (iii) one or more buffers, (iv) one or more tonicity adjusters, (v) one or more surfactants, (vi) flavor, (vii) propellants, and/or (viii) a vehicle or solvent. In some embodiments, all components are compatible with the non-naturally occurring melanocortin analog (i.e., do not react or cause the non-naturally occurring melanocortin analog to react) and are homogeneously dispersed or dissolved uniformly in the composition.

**[0447]** In some embodiments, the pharmaceutically acceptable carriers and/or excipients are isotonic to nasal fluids.

**[0448]** In order to achieve a desirable tonicity, the pharmaceutical composition formulated for intranasal administration may further include a salt such as sodium chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride. In some embodiments, the salt is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 1 mg/mL to 25 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the composition. In some embodiments, the salt is sodium chloride and is present in a concentration of 0.9% by weight.

**[0449]** When the pharmaceutical composition is formulated for intranasal administration, the composition may comprise a pH buffered aqueous solution as previously described.

**[0450]** In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises sodium acetate in a concentration of about 80 mM to about 100 mM. For example, sodium acetate may be present in the pharmaceutical composition in a molar concentration of 80 mM, 81 mM, 82 mM, 83 mM, 84 mM, 85 mM, 86 mM, 87 mM, 88 mM, 89 mM, 90 mM, 91 mM, 92 mM, 93 mM, 94 mM, 95 mM, 96 mM, 97 mM, 98 mM, 99 mM, or 100 mM.

**[0451]** In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises Tris in a concentration of about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, 90 mM, 95 mM, 100 mM, 105 mM, 110 mM, or 120 mM.

**[0452]** Additionally, when the pharmaceutical composition is formulated for intranasal administration, the composition may further comprise a phosphate, e.g., sodium phosphate. In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises sodium phosphate in a molar concentration of about 5 mM to about 700 mM, relative to a total volume of the composition. For example, sodium phosphate may be present in the pharmaceutical composition in a molar concentration of 5 mM to 700 mM, 10 mM to 600 mM, 20 mM to 500 mM, 30 mM to 400 mM, 40 mM to 300 mM, 50 mM to 200 mM, 60 mM to 100 mM, or 70 mM to 80 mM, relative to a total volume of the composition.

**[0453]** In some embodiments, the pharmaceutical composition comprises one or more antioxidants. For example, the pharmaceutical composition may comprise ascorbic acid, cysteine, sodium metabisulfite, propyl gallate, butylated hydroxytoluene, and/or butylated hydroxyanisole.

**[0454]** In some embodiments, the pharmaceutical composition comprises a surfactant, such as a sorbitan ester.

**[0455]** In some embodiments, the pharmaceutical composition comprises a flavoring or scent, such as an aromatic oil.

**[0456]** In some embodiments, the non-naturally occurring melanocortin analog is solubilized or suspended in a solvent or vehicle. The solvent or vehicle may be purified water, ethyl alcohol, and/or propylene glycol. In some embodiments, the pharmaceutical composition comprises between 0.03 wt% and 1 wt% melanocortin analog solubilized or suspended in a solvent or vehicle. For example, the pharmaceutical composition may comprise the non-naturally occurring melanocortin analog in an amount of about 0.03 wt%, about 0.05 wt%, about 0.1 wt%, about 0.15 wt%, about 0.2 wt%, about 0.25 wt%, about 0.3 wt%, about 0.35 wt%, about 0.4 wt%, about 0.45 wt%, about 0.5 wt%, about 0.55 wt%, about 0.6 wt%, about 0.65 wt%, about 0.7 wt%, about 0.75 wt%, about 0.8 wt%, about 0.85 wt%, about 0.9 wt%, about 0.95 wt%, or about 1 wt%.

**[0457]** In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, relative to a total volume of the composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 g/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the pharmaceutical composition. Any of the non-naturally occurring melanocortin analogs and corresponding concentrations described previously with reference to the pharmaceutical composition may be present in the pharmaceutical composition at the same or substantially similar concentrations.

#### *Administration*

**[0458]** The pharmaceutical compositions of the present technology may be administered once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

**[0459]** In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

**[0460]** In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In some embodiments, the administration is performed once monthly.



**[0461]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0462]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and

is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0463]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per

day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0464]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4

times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0465]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks,

once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0466]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1

mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0467]** In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof is administered hourly (such as every hour, every 2 hours, every 4 hours, every 8 hours, etc.), once a day, or twice a day. In some embodiments, the non-naturally occurring melanocortin analog is administered every morning, every evening, or every afternoon. In some embodiments, the non-naturally occurring melanocortin analog is administered before a meal, after a meal, or with a meal.

**[0468]** In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof may be administered as a dosing regimen comprising once, twice, or three times daily administration on a (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five week off; (vi) four weeks of therapy followed by one, two, three, four or five week off; (vii) five weeks of therapy followed by one, two, three, four or five week off; or (viii) monthly schedule. The (i)-(viii) schedules may be repeated 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times or more. In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is administered at various dosages during the dosing regimen (e.g., a first dose with an effective amount of 10 mg/kg and a second dose with an effective amount of 5 mg/kg).

**[0469]** In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is administered once every other day, once every 2 or 3 days, once every third day, once per week, once every other week, once every third week, once every month, once every six weeks, once every other month, once every three months, once every six months, or once per year. Administration of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof at any of the dosing frequencies

of the present technology may be repeated for a total of at least 2 dosages, at least 3 dosages, at least 4 dosages, at least 5 dosages, at least 10 dosages, at least 15 dosages, at least 20 dosages, at least 30 dosages, at least 40 dosages, at least 50 dosages or more. In some embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is the same during a treatment regimen. In other embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is different during a treatment regimen. The non-naturally occurring melanocortin analog or the pharmaceutical composition thereof may be administered even less frequently. Alternatively, the dosage regimen may be decreased or increased from an initial dosing regimen for days, weeks, months, or years. In some embodiments, the dosing regimen is repeated at other intervals.

### ***Dosing***

**[0470]** In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the non-naturally occurring melanocortin analog to the subject in need thereof.

**[0471]** In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least 1 mg, at least 2 mg, at least 3 mg, at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 40 mg, at least 50 mg, at least 60 mg, at least 75 mg, at least 100 mg, at least 125 mg, at least 150 mg, at least 175 mg, at least 200 mg, at least 225 mg, at least 250 mg, at least 275 mg, at least 300 mg, at least 325 mg, at least 350 mg, at least 375 mg, at least 400 mg, at least 425 mg, at least 450 mg, at least 475 mg, or at least 500 mg of the non-naturally occurring melanocortin analog to the subject in need thereof.

**[0472]** In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least about 1 mg, at least about 2 mg, at

least about 3 mg, at least about 5 mg, at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 40 mg, at least about 50 mg, at least about 60 mg, at least about 75 mg, at least about 100 mg, at least about 125 mg, at least about 150 mg, at least about 175 mg, at least about 200 mg, at least about 225 mg, at least about 250 mg, at least about 275 mg, at least about 300 mg, at least about 325 mg, at least about 350 mg, at least about 375 mg, at least about 400 mg, at least about 425 mg, at least about 450 mg, at least about 475 mg, or at least about 500 mg of the non-naturally occurring melanocortin analog to the subject in need thereof.

**[0473]** In some embodiments, the compositions of the present technology are administered to the subject at a dose that is based on the subject's BMI. In some embodiments, two or more doses of the compositions of the present technology are administered to the subject, wherein the two or more doses are titrated (e.g., inversely titrated) based on the subject's BMI at the time of each administration.

**[0474]** In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of about 0.001 mg/kg, about 0.005 mg/kg, about 0.01 mg/kg, about 0.05 mg/kg, about 0.10 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 75 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 225 mg/kg, about 250 mg/kg, about 275 mg/kg, about 300 mg/kg, about 325 mg/kg, about 350 mg/kg, about 375 mg/kg, about 400 mg/kg, about 425 mg/kg, about 450 mg/kg, about 475 mg/kg, or about 500 mg/kg of the non-naturally occurring melanocortin analog to the subject in need thereof.

**[0475]** In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least 0.001 mg/kg, at least 0.005 mg/kg, at least 0.01 mg/kg, at least 0.05 mg/kg, at least 0.10 mg/kg, at least 0.5 mg/kg, at least 1 mg/kg, at least 2 mg/kg, at least 3 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 15 mg/kg, at least 20 mg/kg, at least 25 mg/kg, at least 30 mg/kg, at least 40 mg/kg, at least 50 mg/kg, at least 60 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, at least 175 mg/kg, at least 200 mg/kg, at least 225 mg/kg, at least 250 mg/kg,



at least 275 mg/kg, at least 300 mg/kg, at least 325 mg/kg, at least 350 mg/kg, at least 375 mg/kg, at least 400 mg/kg, at least 425 mg/kg, at least 450 mg/kg, at least 475 mg/kg, or at least 500 mg/kg of the non-naturally occurring melanocortin analog to the subject in need thereof.

In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least about 0.001 mg/kg, at least about 0.005 mg/kg, at least about 0.01 mg/kg, at least about 0.05 mg/kg, at least about 0.10 mg/kg, at least about 0.5 mg/kg, at least about 1 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 5 mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 40 mg/kg, at least about 50 mg/kg, at least about 60 mg/kg, at least about 75 mg/kg, at least about 100 mg/kg, at least about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200 mg/kg, at least about 225 mg/kg, at least about 250 mg/kg, at least about 275 mg/kg, at least about 300 mg/kg, at least about 325 mg/kg, at least about 350 mg/kg, at least about 375 mg/kg, at least about 400 mg/kg, at least about 425 mg/kg, at least about 450 mg/kg, at least about 475 mg/kg, or at least about 500 mg/kg of the non-naturally occurring melanocortin analog to the subject in need thereof.

**[0476]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg to about 500 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg to about 250 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg to about 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

**[0477]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg to at least 500 mg/kg per body weight of the

subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 10 mg/kg to at least 250 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of at least 15 mg/kg to at least 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 20 mg/kg to at least 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

**[0478]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg to at least about 500 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg to at least about 250 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg to at least about 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg to at least about 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

**[0479]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject.

**[0480]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0481]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from at least 0.5 mg/kg to at least 10 mg/kg, at least 1 mg/kg to at least 7.5 mg/kg, or at least 2.5 mg/kg to at least 5 mg/kg per body weight of the subject.

**[0482]** In some embodiments, the non-naturally occurring melanocortin analog is administered about once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0483]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 50 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 250 mg/kg, about 300 mg/kg, about 350 mg/kg, about 400 mg/kg, about 450 mg/kg, or about 500 mg/kg per body weight of the subject once daily.

**[0484]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg, at least 10 mg/kg, at least 15 mg/kg, at least 20 mg/kg, at least 25 mg/kg, at least 30 mg/kg, at least 35 mg/kg, at least 40 mg/kg, at least 50 mg/kg, at least 65 mg/kg, at least 70 mg/kg, at least 75 mg/kg, at least 80 mg/kg, at least 85 mg/kg, at least 90 mg/kg, at least 95 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, at least 175 mg/kg, at least 200 mg/kg, at least 250 mg/kg, at least 300 mg/kg, at least 350 mg/kg, at least 400 mg/kg, at least 450 mg/kg, or at least 500 mg/kg per body weight of the subject once daily.

**[0485]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 35 mg/kg, at least about 40 mg/kg, at least about 50 mg/kg, at least about 65 mg/kg, at least about 70 mg/kg, at least about 75 mg/kg, at least about 80 mg/kg, at least about 85 mg/kg, at least about 90 mg/kg, at least about 95 mg/kg, at least about 100 mg/kg, at least about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200

mg/kg, at least about 250 mg/kg, at least about 300 mg/kg, at least about 350 mg/kg, at least about 400 mg/kg, at least about 450 mg/kg, or at least about 500 mg/kg per body weight of the subject once daily.

**[0486]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject once daily.

**[0487]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg per body weight of the subject once daily.

**[0488]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg per body weight of the subject once daily.

**[0489]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject once daily.

**[0490]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 10 mg/kg per body weight of the subject once daily.

**[0491]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg per body weight of the subject once daily.

**[0492]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject once daily.

**[0493]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 15 mg/kg per body weight of the subject once daily.

**[0494]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg per body weight of the subject once daily.

**[0495]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject once daily.

**[0496]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 20 mg/kg per body weight of the subject once daily.

**[0497]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg per body weight of the subject once daily.

**[0498]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject once daily.

**[0499]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 25 mg/kg per body weight of the subject once daily.

**[0500]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 25 mg/kg per body weight of the subject once daily.

**[0501]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject once daily.

**[0502]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 30 mg/kg per body weight of the subject once daily.

**[0503]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg per body weight of the subject once daily.

**[0504]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject once daily.

**[0505]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 35 mg/kg per body weight of the subject once daily.

**[0506]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 35 mg/kg per body weight of the subject once daily.

**[0507]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject once daily.

**[0508]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 40 mg/kg per body weight of the subject once daily.

In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 40 mg/kg per body weight of the subject once daily.

**[0509]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject once daily.

**[0510]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 50 mg/kg per body weight of the subject once daily.

**[0511]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 50 mg/kg per body weight of the subject once daily.

**[0512]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 50 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 250 mg/kg, about 300 mg/kg, about 350 mg/kg, about 400 mg/kg, about 450 mg/kg, or about 500 mg/kg per body weight of the subject twice daily.

**[0513]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg, at least 10 mg/kg, at least 15 mg/kg, at least 20 mg/kg, at least 25 mg/kg, at least 30 mg/kg, at least 35 mg/kg, at least 40 mg/kg, at least 50 mg/kg, at least 65 mg/kg, at least 70 mg/kg, at least 75 mg/kg, at least 80 mg/kg, at least 85 mg/kg, at least 90 mg/kg, at least 95 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, at least 175 mg/kg, at least 200 mg/kg, at least 250 mg/kg, at least 300 mg/kg, at least 350 mg/kg, at least 400 mg/kg, at least 450 mg/kg, or at least 500 mg/kg per body weight of the subject twice daily.

**[0514]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 35 mg/kg, at least about 40 mg/kg, at least about 50 mg/kg, at least about 65 mg/kg, at least about 70 mg/kg, at least about 75 mg/kg, at least about 80 mg/kg, at least about 85 mg/kg, at least about 90 mg/kg, at least about 95 mg/kg, at least about 100 mg/kg, at least about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200 mg/kg, at least about 250 mg/kg, at least about 300 mg/kg, at least about 350 mg/kg, at least about 400 mg/kg, at least about 450 mg/kg, or at least about 500 mg/kg per body weight of the subject twice daily.

- [0515] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject twice daily.
- [0516] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject twice daily.
- [0517] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject twice daily.
- [0518] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject twice daily.
- [0519] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject twice daily.
- [0520] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject twice daily.
- [0521] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject twice daily.
- [0522] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject twice daily.
- [0523] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject twice daily.
- [0524] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject twice daily.
- [0525] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject twice daily.
- [0526] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject twice daily.
- [0527] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject twice daily.

**[0528]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject twice daily.

**[0529]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject twice daily.

**[0530]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject twice daily.

**[0531]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject twice daily.

**[0532]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject twice daily.

**[0533]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg per body weight of the subject twice daily.

**[0534]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg per body weight of the subject twice daily.

**[0535]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg per body weight of the subject twice daily.

**[0536]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg per body weight of the subject twice daily.

**[0537]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 25 mg/kg per body weight of the subject twice daily.

**[0538]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg per body weight of the subject twice daily.

**[0539]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 35 mg/kg per body weight of the subject twice daily.

**[0540]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 40 mg/kg per body weight of the subject twice daily.



**[0541]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 50 mg/kg per body weight of the subject twice daily.

**[0542]** In some embodiments, the non-naturally occurring melanocortin analog is administered at one or more doses. In some embodiments, the non-naturally occurring melanocortin analog is administered at two or more doses.

**[0543]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a first dose once daily or twice daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a second dose once daily or twice daily.

**[0544]** In some embodiments, the non-naturally occurring melanocortin analog is administered at a first dose once daily for about 5 days to about 10 days. In some embodiments, the non-naturally occurring melanocortin analog is administered at a second dose once daily for about 5 days to about 10 days, after administration of the first dose. In some embodiments, the non-naturally occurring melanocortin analog is administered at a third dose twice daily for about 7 days to about 21 days, after administration of the second dose. In some embodiments, the second dose is greater than the first dose. In some embodiments, the third dose comprises a cumulative dose that is greater than the second dose.

**[0545]** In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg to about 20 mg/kg administered once a day for about 5 days to about 10 days; (ii) at a second dose of about 10 mg/kg to about 40 mg/kg administered once a day after administration of the first dose for about 5 days to about 10 days; (iii) at a third dose of about 5 mg/kg to about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days to about 10 days. In some embodiments, the third dose is administered twice a day for at least about 7 days or more.

**[0546]** In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, or about 20 mg/kg administered once a day for about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or about 10 days; (ii) at a second dose of about 10 mg/kg, about 15

mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, or about 40 mg/kg administered once a day after administration of the first dose about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or about 10 days; (iii) at a third dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, or about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or about 10 days. In some embodiments, the third dose is administered twice a day for at least about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, or about 14 days or more.

**[0547]** In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 15 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 10 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

**[0548]** In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 10 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 20 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 15 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

**[0549]** In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

**[0550]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is administered at least once daily in an amount ranging

from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0551]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0552]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0553]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is administered

at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0554]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0555]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

**[0556]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20

mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount of about 50 mg.

**[0557]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is administered at least once daily in an amount of about 50 mg.

**[0558]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring

melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is administered at least once daily in an amount of about 50 mg.

**[0559]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is administered at least once daily in an amount of about 50 mg.

**[0560]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about

7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is administered at least once daily in an amount of about 50 mg.

**[0561]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is administered at least once daily in an amount of about 50 mg.

**[0562]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 228, 229, 295, 297, 462, 463, 471, 473, 479,

480, 491, and 498 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is administered at least once daily in an amount of about 50 mg.

**[0563]**

**[0564]** In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week,



twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0565]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the

administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0566]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0567]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0568]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per

week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0569]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 268 and 378-380 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed

once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 268 and 378-380 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0570]** In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 and is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition at a dose of about 75 mg in a dose

volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498 is present in the second pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

**[0571]** In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery across the blood brain barrier. In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery across the epithelium. In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery across the epithelium and the blood brain barrier. In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery through the gastrointestinal tract.

**[0572]** *Combination Therapies*

**[0573]** In some embodiments, the weight loss agent is present in a pharmaceutical composition, e.g., the first pharmaceutical composition or the single composition of the present technology. In some embodiments, the non-naturally occurring melanocortin analog is present in a pharmaceutical composition, e.g., the second pharmaceutical composition or the single composition of the present technology.

**[0574]** The weight loss agent and the non-naturally occurring melanocortin analog may be administered concurrently, sequentially, or cyclically. In some embodiments, the weight loss agent and a non-naturally occurring melanocortin agonist are administered concurrently, sequentially, or cyclically. In some embodiments, the weight loss agent and a

non-naturally occurring melanocortin antagonist are administered concurrently, sequentially, or cyclically.

**[0575]** In some embodiments, the weight loss agent and the non-naturally occurring melanocortin analog are administered concurrently. In such embodiments, the weight loss agent and the non-naturally occurring melanocortin analog may be administered concurrently but separately, such as in separate compositions (e.g., the first pharmaceutical composition and the second pharmaceutical composition). When the weight loss agent and the non-naturally occurring melanocortin analog are administered concurrently but separately, the administration may be simultaneous or stepwise. Alternatively, the weight loss agent and the non-naturally occurring melanocortin analog may be formulated in a single composition and may be administered as such.

**[0576]** When the weight loss agent and the non-naturally occurring melanocortin analog are administered to a subject concurrently, administration of the weight loss agent is started at the same time as administration of the non-naturally occurring melanocortin analog. Thus, in a concurrent administration regimen, the subject may not have received any prior treatment with either the weight loss agent or the non-naturally occurring melanocortin analog.

**[0577]** Concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog may include continued administration of both treatments until the desired effect is achieved. In some embodiments, concurrent administration includes beginning treatment with the weight loss agent and the non-naturally occurring melanocortin analog at the same time and continuing administration of the weight loss agent for a full treatment cycle and the non-naturally occurring melanocortin analog for a full treatment cycle. In some embodiments, the full treatment cycle of the weight loss agent is longer than the full treatment cycle of the non-naturally occurring melanocortin analog. In other embodiments, the full treatment cycle of the weight loss agent is shorter than the full treatment cycle of the non-naturally occurring melanocortin analog. Accordingly, although concurrent administration includes beginning treatment with the weight loss agent and the non-naturally occurring melanocortin analog at the same time, administration of the weight

loss agent may be completed before or after administration of the non-naturally occurring melanocortin analog.

**[0578]** Further, when the non-naturally occurring melanocortin analog and the weight loss agent are administered concurrently but separately, the weight loss agent and the non-naturally occurring analog may be administered simultaneously or stepwise. Concurrent stepwise administration may be useful for combination therapies in which the weight loss agent should be administered once a week and the non-naturally occurring melanocortin analog should be administered daily, or with any other regimen where treatment is being carried out simultaneously with the weight loss agent and the non-naturally occurring melanocortin analog, but the administration schedules differ. For example, in concurrent stepwise administration, the weight loss agent may be administered at one time point and the non-naturally melanocortin analog may be administered at a second time point. The time interval between the first time point and the second time point may be about 0.5-1 minutes, 2-3 minutes, 4-5 minutes, 6-8 minutes, 9-10 minutes, 12-15 minutes, 20-25 minutes, 30 to 60 minutes, 1 hour, 1-2 hours, 2-6 hours, 2-12 hours, 12-24 hours, 1-2 days, 2 days, 3 days, 4 days, 5 days, 6 days, or about 1 week, 2 weeks, 3 weeks, one month, or any period of time in between. In some embodiments, the weight loss agent and the non-naturally occurring melanocortin analog are administered less than 15 minutes, less than 30 minutes, less than 45 minutes, less than 1 hour, less than 2 hours, less than 4 hours, less than 8 hours, less than 12 hours, less than 16 hours, less than 20 hours, less than 24 hours, less than 36 hours, or less than 48 hours apart.

**[0579]** In some embodiments, the weight loss agent is administered once weekly and the non-naturally occurring melanocortin analog is administered once, twice, or three times daily. Accordingly, the non-naturally occurring melanocortin analog may be administered 1 day, 2 days, 3 days, 4 days, 5 days, and/or 6 days after the weight loss agent. In other embodiments, the weight loss agent is administered once weekly and the non-naturally occurring melanocortin analog is administered once weekly. When both agents are administered on a weekly basis, the weight loss agent and the non-naturally occurring melanocortin analog may be administered on the same day, 1 day apart, 2 days apart, 3 days apart, 4 days apart, 5 days apart, or 6 days apart. In still other embodiments, the



weight loss agent is administered weekly and the non-naturally occurring melanocortin analog is administered once every 2 weeks, once every 3 weeks, or once monthly. In such embodiments, the non-naturally occurring melanocortin analog may be administered on the same day as the weight loss agent or on a different day than the weight loss agent once every 2 weeks, once every 3 weeks or once monthly.

**[0580]** In some embodiments, the weight loss agent and a non-naturally occurring melanocortin analog are administered concurrently. In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog prevents or reduces loss of lean mass in a subject associated with use of the weight loss agent. In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog promotes fat loss in a subject while maintaining or increasing lean mass in the subject. In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog improves body composition of a subject by promoting fat loss and maintaining or increasing lean mass. In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog accelerates fat loss in a subject while maintaining or increasing lean mass in the subject.

**[0581]** In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog reduces adverse cardiovascular events associated with use of the weight loss agent in a subject. In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog reduces the incidence of myocardial infarction, stroke, sinus tachycardia, sinus bradycardia, and/or angina associated with use of the weight loss agent or the non-naturally occurring melanocortin analog in a subject. In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog reduces hemoglobin A1c levels, decreases inflammation, improves kidney function and/or regulates insulin resistance, and/or myocardial regeneration in the subject. In some embodiments, concurrent administration of the weight loss agent and the non-naturally occurring melanocortin analog treats, prevents, or reduces glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, concurrent administration of the weight loss

agent and the non-naturally occurring melanocortin analog preserves or reduces gastrointestinal effects such as, for example, nausea, vomiting, and diarrhea, associated with the use of a weight loss agent in the subject.

**[0582]** In some embodiments, when the weight loss agent and the non-naturally occurring melanocortin analog are administered to a subject concurrently, a lower dose of the weight loss agent is required to elicit a response in the subject, relative to a dose of the weight loss agent required to elicit the same response without administration of the non-naturally occurring melanocortin analog. Likewise, in some embodiments, when the weight loss agent and the non-naturally occurring melanocortin analog are administered to a subject concurrently, a lower dose of the non-naturally occurring melanocortin analog is required to elicit a response in the subject, relative to a dose of the weight loss agent required to elicit the same response without administration of the weight loss agent.

**[0583]** In other embodiments, the weight loss agent and the non-naturally occurring melanocortin analog are administered sequentially. In sequential administration, the weight loss agent may be administered before the non-naturally occurring melanocortin analog, after the non-naturally occurring melanocortin analog, or both. Likewise, the non-naturally occurring melanocortin analog may be administered before the weight loss agent, after the weight loss agent, or both.

**[0584]** In some embodiments, the non-naturally occurring melanocortin analog is administered before the weight loss agent.

**[0585]** In some embodiments, the non-naturally occurring melanocortin analog is administered before the weight loss agent and after administration of the weight loss agent.

**[0586]** In some embodiments, the non-naturally occurring melanocortin analog is administered before the weight loss agent and during (e.g., coadministration or administration between doses of the weight loss agent) administration of the weight loss agent.

**[0587]** In some embodiments, the non-naturally occurring melanocortin analog is administered before the weight loss agent, during (e.g., coadministration or administration

between doses of the weight loss agent) administration of the weight loss agent, and after administration of the weight loss agent.

**[0588]** In some embodiments, the non-naturally occurring melanocortin analog is administered during (e.g., coadministration or administration between doses of the weight loss agent) administration of the weight loss agent and after administration of the weight loss agent.

**[0589]** In some embodiments, the non-naturally occurring melanocortin analog is administered after administration of the weight loss agent.

**[0590]** In some embodiments, the non-naturally occurring melanocortin analog is administered about 30 second, about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 1 week, about 2 weeks, about 4 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 1 year, or about 2 years before administration of the weight loss agent.

**[0591]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least 30 second, at least 1 minute, at least 2 minutes, at least 3 minutes, at least 4 minutes, at least 5 minutes, at least 10 minutes, at least 15 minutes, at least 20 minutes, at least 30 minutes, at least 45 minutes, at least 1 hour, at least 1.5 hours, at least 2 hours, at least 2.5 hours, at least 5 hours, at least 10 hours, at least 12 hours, at least 24 hours, at least 36 hours, at least 48 hours, at least 3 days, at least 4 days, at least 5 days, at least 1 week, at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 1 year, or at least 2 years before administration of the weight loss agent.

**[0592]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least about 30 second, at least about 1 minute, at least about 2 minutes, at

least about 3 minutes, at least about 4 minutes, at least about 5 minutes, at least about 10 minutes, at least about 15 minutes, at least about 20 minutes, at least about 30 minutes, at least about 45 minutes, at least about 1 hour, at least about 1.5 hours, at least about 2 hours, at least about 2.5 hours, at least about 5 hours, at least about 10 hours, at least about 12 hours, at least about 24 hours, at least about 36 hours, at least about 48 hours, at least about 3 days, at least about 4 days, at least about 5 days, at least about 1 week, at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 1 year, or at least about 2 years before administration of the weight loss agent.

**[0593]** In some embodiments, the non-naturally occurring melanocortin analog is administered about 30 second, about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 1 week, about 2 weeks, about 4 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 1 year, or about 2 years after administration of the weight loss agent.

**[0594]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least 30 second, at least 1 minute, at least 2 minutes, at least 3 minutes, at least 4 minutes, at least 5 minutes, at least 10 minutes, at least 15 minutes, at least 20 minutes, at least 30 minutes, at least 45 minutes, at least 1 hour, at least 1.5 hours, at least 2 hours, at least 2.5 hours, at least 5 hours, at least 10 hours, at least 12 hours, at least 24 hours, at least 36 hours, at least 48 hours, at least 3 days, at least 4 days, at least 5 days, at least 1 week, at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 1 year, or at least 2 years after administration of the weight loss agent.

**[0595]** In some embodiments, the non-naturally occurring melanocortin analog is administered at least about 30 second, at least about 1 minute, at least about 2 minutes, at least about 3 minutes, at least about 4 minutes, at least about 5 minutes, at least about 10 minutes, at least about 15 minutes, at least about 20 minutes, at least about 30 minutes, at least about 45 minutes, at least about 1 hour, at least about 1.5 hours, at least about 2 hours, at least about 2.5 hours, at least about 5 hours, at least about 10 hours, at least about 12 hours, at least about 24 hours, at least about 36 hours, at least about 48 hours, at least about 3 days, at least about 4 days, at least about 5 days, at least about 1 week, at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 1 year, or at least about 2 years after administration of the weight loss agent.

**[0596]** In sequential administration of the weight loss agent and the non-naturally occurring melanocortin analog, administration of one treatment is completed before administration of the other treatment begins. For example, in sequential administration, when the weight loss agent is administered before the non-naturally occurring melanocortin analog, treatment with the weight loss agent is completed before the non-naturally occurring melanocortin analog is administered to the subject. Likewise, in sequential administration, when the non-naturally occurring melanocortin analog is administered before the weight loss agent, treatment with the non-naturally occurring melanocortin analog is completed before the weight loss agent is administered to the subject.

**[0597]** When the non-naturally occurring melanocortin analog and the weight loss agent are administered sequentially, the administration of the second treatment may begin any amount of time after administration of the first treatment has completed. In embodiments in which the weight loss agent administered first and the non-naturally occurring melanocortin analog is administered second, the interval of time between completing administration of the weight loss agent (e.g., GLP-1 receptor agonist) and beginning administration of the non-naturally occurring melanocortin analog may be about 0.5-1 minutes, 2-3 minutes, 4-5 minutes, 6-8 minutes, 9-10 minutes, 12-15 minutes, 20-25 minutes, 30 to 60 minutes, 1 hour, 1-2 hours, 2-6 hours, 2-12 hours, 12-24 hours, 1-2 days,

2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 15 weeks, 20 weeks, 26 weeks, 52 weeks, 11-15 weeks, 15-20 weeks, 20-30 weeks, 30-40 weeks, 40-50 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 1 year, 2 years, or any period of time in between. The same interval of time may be applied when the non-naturally occurring melanocortin analog is administered first and the weight loss agent is administered second.

**[0598]** In some embodiments, the weight loss agent and a non-naturally occurring melanocortin analog are administered sequentially. In some embodiments, the weight loss agent is administered first and the non-naturally occurring melanocortin analog is administered second. In some embodiments, the non-naturally occurring melanocortin analog is administered first and the weight loss agent is administered second.

**[0599]** In some embodiments, sequential administration of the weight loss agent and the melanocortin antagonist prevents or reduces loss of lean mass in a subject associated with use of the weight loss agent. In some embodiments, sequential administration of the weight loss agent and the melanocortin antagonist promotes fat loss in a subject while maintaining or increasing lean mass in the subject. In some embodiments, sequential administration of the weight loss agent and the melanocortin antagonist improves body composition of a subject by promoting fat loss and maintaining or increasing lean mass. In some embodiments, sequential administration of the weight loss agent and the non-naturally occurring melanocortin analog accelerates fat loss in a subject while maintaining or increasing lean mass in the subject.

**[0600]** In some embodiments, sequential administration of the weight loss agent and the non-naturally occurring melanocortin analog reduces adverse cardiovascular events associated with use of the weight loss agent in a subject. In some embodiments, sequential administration of the weight loss agent and the non-naturally occurring melanocortin analog reduces the incidence of myocardial infarction, stroke, sinus tachycardia, sinus bradycardia, and/or angina associated with use of the weight loss agent or the non-naturally occurring melanocortin analog in a subject. In some embodiments, sequential administration of the weight loss agent and the non-naturally occurring melanocortin analog reduces hemoglobin

A1c levels, decreases inflammation, improves kidney function and/or regulates insulin resistance, and/or myocardial regeneration in the subject. In some embodiments, sequential administration of the weight loss agent and the non-naturally occurring melanocortin analog treats, prevents, or reduces glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, sequential administration of the weight loss agent and the non-naturally occurring melanocortin analog preserves reduces gastrointestinal effects such as, for example, nausea, vomiting, and diarrhea, associated with the use of a weight loss agent in the subject.

**[0601]** In some embodiments, when the weight loss agent and the non-naturally occurring melanocortin analog are administered to a subject sequentially, a lower dose of the weight loss agent is required to elicit a response in the subject, relative to a dose of the weight loss agent required to elicit the same response without administration of the non-naturally occurring melanocortin analog. Likewise, in some embodiments, when the weight loss agent and the non-naturally occurring melanocortin analog are administered to a subject sequentially, a lower dose of the non-naturally occurring melanocortin analog is required to elicit a response in the subject, relative to a dose of the weight loss agent required to elicit the same response without administration of the weight loss agent.

**[0602]** In still other embodiments, the weight loss agent and the non-naturally occurring melanocortin analog may be administered cyclically. For example, in cyclical administration, the weight loss agent may be administered for one cycle, followed by administration of the non-naturally occurring melanocortin analog for one cycle, followed by administration of the weight loss agent for a second cycle, followed by administration of the non-naturally occurring melanocortin analog for a second cycle, and so on.

**[0603]** In some embodiments, the weight loss agent is administered first, and after a period of time the non-naturally occurring melanocortin analog is administered. Once administration of the non-naturally occurring melanocortin analog is started, the weight loss agent and the non-naturally occurring melanocortin analog may be administered concurrently (e.g., simultaneously or stepwise). When the weight loss agent is administered prior to administration of the non-naturally occurring melanocortin analog, the weight loss agent may be administered for one or more doses, one or more weeks, one or more cycles,

or until treatment is completed with the weight loss agent, before the non-naturally occurring melanocortin analog is administered to the subject. In some embodiments, only one dose of the weight loss agent is administered before the non-naturally occurring melanocortin analog is administered. In some embodiments, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more doses of the weight loss agent are administered before the non-naturally occurring melanocortin analog is administered. In some embodiments, the period of time that the weight loss agent is administered alone is about 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 1.5 years, 2 years, 3 years, 4 years or 5 years, or any period of time in between.

**[0604]** In some embodiments, the weight loss agent is administered prior to administration of the non-naturally occurring melanocortin analog, and when administration of the non-naturally occurring melanocortin analog begins, administration of the weight loss agent is paused until administration of the non-naturally occurring melanocortin analog is completed. In such embodiments, once administration of the non-naturally occurring melanocortin analog is completed, administration of the weight loss agent may be resumed. In some embodiments, administration of the non-naturally occurring melanocortin analog is completed after about 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 1.5 years, 2 years, 3 years, 4 years or 5 years, or any period of time in between. The weight loss agent and non-naturally occurring melanocortin analog may be administered as such for any number of iterations.

**[0605]** In some embodiments, the weight loss agent is administered to a subject without the non-naturally occurring melanocortin analog until the subject no longer responds to the weight loss agent alone, e.g., when the subject stops losing body weight and/or fat mass. Alternatively, in some embodiments, the non-naturally melanocortin analog is administered to the subject while the subject continues to respond to the weight loss agent, e.g., when the subject is still losing body weight and/or fat mass. Administration of the non-naturally occurring melanocortin analog with the weight loss agent may elicit an additive or synergistic effect on weight loss in the subject, and therefore, may require a reduced dose of the weight loss agent to elicit a response in the subject. Accordingly, in some embodiments, when the



non-naturally melanocortin analog is administered to the subject while the subject continues to respond to the weight loss agent, the dose of the weight loss agent may be reduced compared to a dose of the weight loss agent required to elicit a response in the subject without the non-naturally occurring melanocortin analog.

**[0606]** In some embodiments, when the weight loss agent is first administered to the subject without the non-naturally occurring melanocortin analog, the subject failed to lose sufficient body weight following administration of the weight loss agent. In some embodiments, the subject failed to lose any body weight following administration of the weight loss agent.

**[0607]** In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the weight loss agent. Once administration of the weight loss agent is started, the non-naturally occurring melanocortin analog and the weight loss agent may be administered concurrently (e.g., simultaneously or stepwise). When the non-naturally occurring melanocortin analog is administered prior to administration of the weight loss agent, the non-naturally occurring melanocortin analog may be administered for one or more doses, one or more weeks, one or more cycles, or until treatment with the non-naturally occurring melanocortin analog is complete, before the weight loss agent is administered to the subject. In some embodiments, only one dose of the non-naturally occurring melanocortin analog is administered before the weight loss agent is administered. In some embodiments, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more doses of the non-naturally occurring melanocortin analog are administered before the weight loss agent is administered. In some embodiments, the period of time that the non-naturally occurring melanocortin analog is administered alone is about 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 1.5 years, 2 years, 3 years, 4 years or 5 years, or any period of time in between.

**[0608]** In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the weight loss agent, and when administration of the weight loss agent begins, administration of the non-naturally occurring melanocortin analog is paused until administration of the weight loss is completed. In such embodiments, once

administration of the non-naturally occurring melanocortin analog is completed, administration of the weight loss agent may be resumed. In some embodiments, administration of the non-naturally occurring melanocortin analog is completed after about 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 1.5 years, 2 years, 3 years, 4 years or 5 years, or any period of time in between.

**[0609]** The weight loss agent may be administered at a treatment dose for a period of time to achieve a desired effect, e.g., body weight and/or fat mass loss, and then, once the desired effect is achieved, the weight loss agent may be administered at a maintenance dose to maintain the effect. In some embodiments, administration of the non-naturally occurring melanocortin analog is started before the weight loss agent is administered at the maintenance dose. In other embodiments, administration of the non-naturally occurring melanocortin analog is started when the weight loss agent is administered at the maintenance dose. In still other embodiments, administration of the non-naturally occurring melanocortin analog is started at some point after the weight loss agent is administered at the maintenance dose.

**[0610]** When the non-naturally occurring melanocortin analog is administered while the weight loss agent is administered at the treatment dose, the treatment dose of the weight loss agent may be reduced compared to the treatment dose required for the weight loss agent administered alone. Likewise, when the non-naturally occurring melanocortin analog is administered when the weight loss agent is administered at the maintenance dose, the maintenance dose of the weight loss agent may be reduced compared to the maintenance dose required for the weight loss agent administered alone.

**[0611]** As used herein, a “treatment dose” and a “maintenance dose” refer to the amount of the active ingredient administered to a subject. Accordingly, when the weight loss agent is a salt compound, the dose, i.e., therapeutically effective dose or maintenance dose, administered to the subject is equivalent to the amount of active substance that the subject will receive from that dose.

**[0612]** In some embodiments, a treatment dose of the weight loss agent is administered to a subject with a metabolic dysfunction. In some embodiments, a treatment

dose of the weight loss agent or a pharmaceutical composition thereof (e.g., the first pharmaceutical composition) is administered at least once per week.

**[0613]** In some embodiments, a maintenance dose of the weight loss agent is administered to a subject with a metabolic dysfunction. In some embodiments, a maintenance dose of the weight loss agent of a pharmaceutical composition thereof (e.g., the first pharmaceutical composition) is administered at least once per week.

**[0614]** In some embodiments, the weight loss agent is a GLP-1 receptor agonist and is administered at a dose of about 0.0005 mg to about 100 mg, about 0.001 mg to about 50 mg, about 0.05 mg to about 25 mg, 0.01 mg to about 10 mg, about 0.05 mg to about 8 mg, about 0.1 mg to about 5 mg, about 0.2 to about 3 mg, or about 0.25 to about 2.5 mg once per week.

**[0615]** In some embodiments, the weight loss agent is a GLP-1 receptor agonist and is administered at a dose of at least 0.0005 mg to at least 100 mg, at least 0.001 mg to at least 50 mg, at least 0.05 mg to at least 25 mg, 0.01 mg to at least 10 mg, at least 0.05 mg to at least 8 mg, at least 0.1 mg to at least 5 mg, at least 0.2 to at least 3 mg, or at least 0.25 to at least 2.5 mg once per week.

**[0616]** In some embodiments, the weight loss agent is a GLP-1 receptor agonist and is administered at a dose of at least about 0.0005 mg to at least about 100 mg, at least about 0.001 mg to at least about 50 mg, at least about 0.05 mg to at least about 25 mg, 0.01 mg to at least about 10 mg, at least about 0.05 mg to at least about 8 mg, at least about 0.1 mg to at least about 5 mg, at least about 0.2 to at least about 3 mg, or at least about 0.25 to at least about 2.5 mg once per week.

**[0617]** In some embodiments, the weight loss agent is semaglutide and is administered at a dose ranging from about 0.01 mg to about 10 mg, about 0.05 mg to about 8 mg, about 0.1 mg to about 5 mg, about 0.2 to about 3 mg, or about 0.25 to about 2.5 mg once per week. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of about 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of less than about 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week.

**[0618]** In some embodiments, the weight loss agent is semaglutide and is administered at a dose ranging from at least 0.01 mg to at least 10 mg, at least 0.05 mg to at least 8 mg, at least 0.1 mg to at least 5 mg, at least 0.2 to at least 3 mg, or at least 0.25 to at least 2.5 mg once per week. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of at least 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of less than at least 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week

**[0619]** In some embodiments, the weight loss agent is semaglutide and is administered at a dose ranging from at least about 0.01 mg to at least about 10 mg, at least about 0.05 mg to at least about 8 mg, at least about 0.1 mg to at least about 5 mg, at least about 0.2 to at least about 3 mg, or at least about 0.25 to at least about 2.5 mg once per week. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of at least about 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of less than at least about 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week

**[0620]** In some embodiments, the weight loss agent is Ozempic® and is administered according to the label instructions. In some embodiments, the weight loss agent is Ozempic® and is administered less frequently and/or at a lower dose than specified on the label instructions. In some embodiments, the weight loss agent is Wegovy® and is administered according to the label instructions. In some embodiments, the weight loss agent is Wegovy® and is administered less frequently and/or at a lower dose than specified on the label instructions.

**[0621]** In some embodiments, about the weight loss agent is semaglutide and is administered at a dose of about 0.5 mg to about 40 mg once daily. In some embodiments, about the weight loss agent is semgalutide and is administered at a dose of about 0.5 mg to 40 mg, about 0.5 mg to 30 mg, about 1 mg to 30 mg, about 0.5 mg to 20 mg, about 1 mg to 20 mg, about 2 mg to 20 mg, about 0.5 mg to 15 mg, about 1 mg to 15 mg, about 2 mg to 15 mg, about 3 mg to 15 mg, about 5 mg to 15 mg, about 0.5 mg to 10 mg, about 1 mg to 10 mg, about or 5 mg to 10 mg once daily. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of about 3 mg, about 7mg or 14 mg once daily.

In some embodiments, the weight loss agent is semaglutide and is administered at a dose of less than 3 mg, about 7mg or 14 mg once daily.

**[0622]** In some embodiments, at least the weight loss agent is semaglutide and is administered at a dose of at least 0.5 mg to at least 40 mg once daily. In some embodiments, at least the weight loss agent is semgalutide and is administered at a dose of at least 0.5 mg to 40 mg, at least 0.5 mg to 30 mg, at least 1 mg to 30 mg, at least 0.5 mg to 20 mg, at least 1 mg to 20 mg, at least 2 mg to 20 mg, at least 0.5 mg to 15 mg, at least 1 mg to 15 mg, at least 2 mg to 15 mg, at least 3 mg to 15 mg, at least 5 mg to 15 mg, at least 0.5 mg to 10 mg, at least 1 mg to 10 mg, at least or 5 mg to 10 mg once daily. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of at least 3 mg, at least 7mg or 14 mg once daily. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of less than 3 mg, at least 7mg or 14 mg once daily.

**[0623]** In some embodiments, the weight loss agent is semaglutide and is administered at a dose of at least about 0.5 mg to at least about 40 mg once daily. In some embodiments, the weight loss agent is semgalutide and is administered at a dose of at least about 0.5 mg to 40 mg, at least about 0.5 mg to 30 mg, at least about 1 mg to 30 mg, at least about 0.5 mg to 20 mg, at least about 1 mg to 20 mg, at least about 2 mg to 20 mg, at least about 0.5 mg to 15 mg, at least about 1 mg to 15 mg, at least about 2 mg to 15 mg, at least about 3 mg to 15 mg, at least about 5 mg to 15 mg, at least about 0.5 mg to 10 mg, at least about 1 mg to 10 mg, at least about or 5 mg to 10 mg once daily. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of at least about 3 mg, at least about 7mg or 14 mg once daily. In some embodiments, the weight loss agent is semaglutide and is administered at a dose of less than 3 mg, at least about 7mg or 14 mg once daily.

**[0624]** In some embodiments, the weight loss agent is Rybelsus® and is administered according to the label instructions. In some embodiments, the weight loss agent is Rybelsus® and is administered less frequently and/or at a lower dose than specified on the label instructions.

**[0625]** In some embodiments, the weight loss agent is exenatide and is administered at a dose of about 0.5 µg to about 100 µg twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of about 0.5 µg to about 100 µg, about

1.0 µg mg to 90 µg, about 1.1 µg to 80 µg, about 1.2 µg to 70 µg, about 1.3 µg to 60 µg, about 1.4 µg to 50 µg, about 1.5 µg to 45 µg, about 1.6 µg to 40 µg, about 1.7 µg to 35 µg, about 1.8 µg to 30 µg, about 1.9 µg to 25 µg, about 2.0 µg to 20 µg, about 2.1 µg to 19 µg, about 2.2 µg to 18 µg, about 2.3 µg to 17 µg, about 2.4 µg to 16 µg, about 2.5 µg to 15 µg, about or 5 µg to 10 µg twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of about 5 µg or 10 µg, about twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of less than 5 µg or 10 µg, about twice daily.

**[0626]** In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least 0.5 µg to at least 100 µg twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least 0.5 µg to at least 100 µg, at least 1.0 µg mg to 90 µg, at least 1.1 µg to 80 µg, at least 1.2 µg to 70 µg, at least 1.3 µg to 60 µg, at least 1.4 µg to 50 µg, at least 1.5 µg to 45 µg, at least 1.6 µg to 40 µg, at least 1.7 µg to 35 µg, at least 1.8 µg to 30 µg, at least 1.9 µg to 25 µg, at least 2.0 µg to 20 µg, at least 2.1 µg to 19 µg, at least 2.2 µg to 18 µg, at least 2.3 µg to 17 µg, at least 2.4 µg to 16 µg, at least 2.5 µg to 15 µg, at least or 5 µg to 10 µg twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least 5 µg or 10 µg, at least twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of less than 5 µg or 10 µg, at least twice daily.

**[0627]** In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least about 0.5 µg to at least about 100 µg twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least about 0.5 µg to at least about 100 µg, at least about 1.0 µg mg to 90 µg, at least about 1.1 µg to 80 µg, at least about 1.2 µg to 70 µg, at least about 1.3 µg to 60 µg, at least about 1.4 µg to 50 µg, at least about 1.5 µg to 45 µg, at least about 1.6 µg to 40 µg, at least about 1.7 µg to 35 µg, at least about 1.8 µg to 30 µg, at least about 1.9 µg to 25 µg, at least about 2.0 µg to 20 µg, at least about 2.1 µg to 19 µg, at least about 2.2 µg to 18 µg, at least about 2.3 µg to 17 µg, at least about 2.4 µg to 16 µg, at least about 2.5 µg to 15 µg, at least about or 5 µg to 10 µg twice daily. In some embodiments, the weight loss agent is exenatide and is administered

at a dose of at least about 5 µg or 10 µg, at least about twice daily. In some embodiments, the weight loss agent is exenatide and is administered at a dose of less than 5 µg or 10 µg, at least about twice daily.

**[0628]** In some embodiments, the weight loss agent is Byetta® and is administered according to the label instructions. In some embodiments, the weight loss agent is Byetta® and is administered less frequently and/or at a lower dose than specified on the label instructions.

**[0629]** In some embodiments, the weight loss agent is exenatide and is administered at a dose of about 0.5 mg to about 50 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of about 0.5 mg to about 50 mg, about 0.75 mg to about 40 mg, about 1 mg to about 30 mg, about 1.25 mg to about 20 mg, about 1.5 mg to about 15 mg, about 1.75 mg to about 10 mg, about 2 mg to about 5 mg, about 0.5 mg to about 5 mg, about 0.75 mg to about 5 mg, about 1 mg to about 5 mg, about 1.25 mg to about 5 mg, about 1.5 mg to about 5 mg, about 1.75 mg to about 5 mg, about 0.5 mg to about 2 mg, about 1 mg to about 2 mg, or about 1.5 mg to about 2 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of about 2 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of less than about 2 mg once per week.

**[0630]** In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least 0.5 mg to at least 50 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least 0.5 mg to at least 50 mg, at least 0.75 mg to at least 40 mg, at least 1 mg to at least 30 mg, at least 1.25 mg to at least 20 mg, at least 1.5 mg to at least 15 mg, at least 1.75 mg to at least 10 mg, at least 2 mg to at least 5 mg, at least 0.5 mg to at least 5 mg, at least 0.75 mg to at least 5 mg, at least 1 mg to at least 5 mg, at least 1.25 mg to at least 5 mg, at least 1.5 mg to at least 5 mg, at least 1.75 mg to at least 5 mg, at least 0.5 mg to at least 2 mg, at least 1 mg to at least 2 mg, or at least 1.5 mg to at least 2 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least 2 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of less than at least 2 mg once per week.

**[0631]** In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least about 0.5 mg to at least about 50 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least about 0.5 mg to at least about 50 mg, at least about 0.75 mg to at least about 40 mg, at least about 1 mg to at least about 30 mg, at least about 1.25 mg to at least about 20 mg, at least about 1.5 mg to at least about 15 mg, at least about 1.75 mg to at least about 10 mg, at least about 2 mg to at least about 5 mg, at least about 0.5 mg to at least about 5 mg, at least about 0.75 mg to at least about 5 mg, at least about 1 mg to at least about 5 mg, at least about 1.25 mg to at least about 5 mg, at least about 1.5 mg to at least about 5 mg, at least about 1.75 mg to at least about 5 mg, at least about 0.5 mg to at least about 2 mg, at least about 1 mg to at least about 2 mg, or at least about 1.5 mg to at least about 2 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of at least about 2 mg once per week. In some embodiments, the weight loss agent is exenatide and is administered at a dose of less than at least about 2 mg once per week.

**[0632]** In some embodiments, the weight loss agent is Bydureon® and is administered according to the label instructions. In some embodiments, the weight loss agent is Bydureon® and is administered less frequently and/or at a lower dose than specified on the label instructions.

**[0633]** In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of about 0.05 mg to about 50 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of about 0.05 mg to about 50 mg, about 0.1 mg to about 40 mg, about 0.25 mg to about 30 mg, about 0.5 mg to about 20 mg, about 0.5 mg to about 15 mg, about 0.75 mg to about 15 mg, about 0.5 mg to about 10 mg, about 0.75 mg to about 10 mg, about 1 mg to about 10 mg, about 0.5 mg to about 5 mg, about 0.75 mg to about 5 mg, about 1 mg to about 5 mg, about 1.5 mg to about 5 mg, or about 2 mg to about 5 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of about 0.75 mg, about 1.5 mg, about 3.0 mg, or about 4.5 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of less than about 0.75 mg, about 1.5 mg, about 3.0 mg, or about 4.5 mg once per week.



**[0634]** In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of at least 0.05 mg to at least 50 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of at least 0.05 mg to at least 50 mg, at least 0.1 mg to at least 40 mg, at least 0.25 mg to at least 30 mg, at least 0.5 mg to at least 20 mg, at least 0.5 mg to at least 15 mg, at least 0.75 mg to at least 15 mg, at least 0.5 mg to at least 10 mg, at least 0.75 mg to at least 10 mg, at least 1 mg to at least 10 mg, at least 0.5 mg to at least 5 mg, at least 0.75 mg to at least 5 mg, at least 1 mg to at least 5 mg, at least 1.5 mg to at least 5 mg, or at least 2 mg to at least 5 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of at least 0.75 mg, at least 1.5 mg, at least 3.0 mg, or at least 4.5 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of less than at least 0.75 mg, at least 1.5 mg, at least 3.0 mg, or at least 4.5 mg once per week.

**[0635]** In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of at least about 0.05 mg to at least about 50 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of at least about 0.05 mg to at least about 50 mg, at least about 0.1 mg to at least about 40 mg, at least about 0.25 mg to at least about 30 mg, at least about 0.5 mg to at least about 20 mg, at least about 0.5 mg to at least about 15 mg, at least about 0.75 mg to at least about 15 mg, at least about 0.5 mg to at least about 10 mg, at least about 0.75 mg to at least about 10 mg, at least about 1 mg to at least about 10 mg, at least about 0.5 mg to at least about 5 mg, at least about 0.75 mg to at least about 5 mg, at least about 1 mg to at least about 5 mg, at least about 1.5 mg to at least about 5 mg, or at least about 2 mg to at least about 5 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of at least about 0.75 mg, at least about 1.5 mg, at least about 3.0 mg, or at least about 4.5 mg once per week. In some embodiments, the weight loss agent is dulaglutide and is administered at a dose of less than at least about 0.75 mg, at least about 1.5 mg, at least about 3.0 mg, or at least about 4.5 mg once per week.

**[0636]** In some embodiments, the weight loss agent is Trulicity® and is administered according to the label instructions. In some embodiments, the weight loss agent is Trulicity®

and is administered less frequently and/or at a lower dose than specified on the label instructions.

**[0637]** In some embodiments, the weight loss agent is orforglipron and is administered at a dose of about 0.01 mg to about 100 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of about 0.01 mg to about 100 mg, about 0.05 mg to about 90 mg, about 0.1 mg to about 80 mg, about 0.2 mg to about 70 mg, about 0.3 mg to about 60 mg, about 0.4 mg to about 50 mg, about 0.5 mg to about 45 mg, about 0.6 mg to about 40 mg, about 0.7 mg to about 35 mg, about 0.8 mg to about 30 mg, about 0.9 mg to about 25 mg, about 1.0 mg to about 20 mg, about 1.1 mg to about 18 mg, about 1.2 mg to about 16 mg, about 1.3 mg to about 14 mg, about 1.4 mg to about 12 mg, or about 1.5 mg to about 10 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of about 2 mg, about 4 mg, about 5 mg, about 6 mg, about 8 mg, about 12 mg, about 16 mg, or about 24 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of less than about 2 mg, about 4 mg, about 5 mg, about 6 mg, about 8 mg, about 12 mg, about 16 mg, or about 24 mg once daily.

**[0638]** In some embodiments, the weight loss agent is orforglipron and is administered at a dose of at least 0.01 mg to at least 100 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of at least 0.01 mg to at least 100 mg, at least 0.05 mg to at least 90 mg, at least 0.1 mg to at least 80 mg, at least 0.2 mg to at least 70 mg, at least 0.3 mg to at least 60 mg, at least 0.4 mg to at least 50 mg, at least 0.5 mg to at least 45 mg, at least 0.6 mg to at least 40 mg, at least 0.7 mg to at least 35 mg, at least 0.8 mg to at least 30 mg, at least 0.9 mg to at least 25 mg, at least 1.0 mg to at least 20 mg, at least 1.1 mg to at least 18 mg, at least 1.2 mg to at least 16 mg, at least 1.3 mg to at least 14 mg, at least 1.4 mg to at least 12 mg, or at least 1.5 mg to at least 10 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of at least 2 mg, at least 4 mg, at least 5 mg, at least 6 mg, at least 8 mg, at least 12 mg, at least 16 mg, or at least 24 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of less than at least 2 mg, at least 4 mg,

at least 5 mg, at least 6 mg, at least 8 mg, at least 12 mg, at least 16 mg, or at least 24 mg once daily.

**[0639]** In some embodiments, the weight loss agent is orforglipron and is administered at a dose of at least about 0.01 mg to at least about 100 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of at least about 0.01 mg to at least about 100 mg, at least about 0.05 mg to at least about 90 mg, at least about 0.1 mg to at least about 80 mg, at least about 0.2 mg to at least about 70 mg, at least about 0.3 mg to at least about 60 mg, at least about 0.4 mg to at least about 50 mg, at least about 0.5 mg to at least about 45 mg, at least about 0.6 mg to at least about 40 mg, at least about 0.7 mg to at least about 35 mg, at least about 0.8 mg to at least about 30 mg, at least about 0.9 mg to at least about 25 mg, at least about 1.0 mg to at least about 20 mg, at least about 1.1 mg to at least about 18 mg, at least about 1.2 mg to at least about 16 mg, at least about 1.3 mg to at least about 14 mg, at least about 1.4 mg to at least about 12 mg, or at least about 1.5 mg to at least about 10 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of at least about 2 mg, at least about 4 mg, at least about 5 mg, at least about 6 mg, at least about 8 mg, at least about 12 mg, at least about 16 mg, or at least about 24 mg once daily. In some embodiments, the weight loss agent is orforglipron and is administered at a dose of less than at least about 2 mg, at least about 4 mg, at least about 5 mg, at least about 6 mg, at least about 8 mg, at least about 12 mg, at least about 16 mg, or at least about 24 mg once daily.

**[0640]** In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist and is administered at a dose of about 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 1.5 mg to about 30 mg, about 2 mg to about 20 mg, or about 2.5 mg to about 15 mg once per week.

**[0641]** In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist and is administered at a dose of at least 0.5 mg to at least 50 mg, at least 1 mg to at least 40 mg, at least 1.5 mg to at least 30 mg, at least 2 mg to at least 20 mg, or at least 2.5 mg to at least 15 mg once per week.

**[0642]** In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist and is administered at a dose of at least about 0.5 mg to at least about 50 mg, at

least about 1 mg to at least about 40 mg, at least about 1.5 mg to at least about 30 mg, at least about 2 mg to at least about 20 mg, or at least about 2.5 mg to at least about 15 mg once per week.

**[0643]** In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of about 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 1.5 mg to about 30 mg, about 2 mg to about 20 mg, or about 2.5 mg to about 15 mg once per week. In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg, or about 15 mg once per week. In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of less than about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg, or about 15 mg once per week.

**[0644]** In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of at least 0.5 mg to at least 50 mg, at least 1 mg to at least 40 mg, at least 1.5 mg to at least 30 mg, at least 2 mg to at least 20 mg, or at least 2.5 mg to at least 15 mg once per week. In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of at least 2.5 mg, at least 5 mg, at least 7.5 mg, at least 10 mg, at least 12.5 mg, or at least 15 mg once per week. In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of less than at least 2.5 mg, at least 5 mg, at least 7.5 mg, at least 10 mg, at least 12.5 mg, or at least 15 mg once per week.

**[0645]** In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of at least about 0.5 mg to at least about 50 mg, at least about 1 mg to at least about 40 mg, at least about 1.5 mg to at least about 30 mg, at least about 2 mg to at least about 20 mg, or at least about 2.5 mg to at least about 15 mg once per week. In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of at least about 2.5 mg, at least about 5 mg, at least about 7.5 mg, at least about 10 mg, at least about 12.5 mg, or at least about 15 mg once per week. In some embodiments, the weight loss agent is tirzepatide and is administered at a dose of less than at least about 2.5 mg, at least about 5 mg, at least about 7.5 mg, at least about 10 mg, at least about 12.5 mg, or at least about 15 mg once per week.

**[0646]** In some embodiments, the weight loss agent is Mounjaro™ and is administered according to the label instructions. In some embodiments, the weight loss agent is Mounjaro™ and is administered less frequently and/or at a lower dose than specified on the label instructions. In some embodiments, the weight loss agent is Zepbound™ and is administered according to the label instructions. In some embodiments, the weight loss agent is Zepbound™ and is administered less frequently and/or at a lower dose than specified on the label instructions.

**[0647]** In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is administered at a dose of about 0.5 mg to about 50 mg once per week. In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is administered at a dose of about 0.5 mg to about 50 mg, about 1 mg to about 50 mg, about 5 mg to about 50 mg, about 0.5 mg to about 40 mg, about 1 mg to about 40 mg, about 5 mg to about 40 mg, about 0.5 mg to about 30 mg, about 1 mg to about 30 mg, about 5 mg to about 30 mg, about 0.5 mg to about 20 mg, about 1 mg to about 20 mg, about 2 mg to about 20 mg, about 5 mg to about 20 mg, about 0.5 mg to about 15 mg, about 1 mg to about 15 mg, about 2 mg to about 15 mg, about 3 mg to about 15 mg, about 5 mg to about 15 mg, about 0.5 mg to about 10 mg, about 1 mg to about 10 mg, or about 5 mg to about 10 mg once per week.

**[0648]** In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is administered at a dose of at least 0.5 mg to at least 50 mg once per week. In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is administered at a dose of at least 0.5 mg to at least 50 mg, at least 1 mg to at least 50 mg, at least 5 mg to at least 50 mg, at least 0.5 mg to at least 40 mg, at least 1 mg to at least 40 mg, at least 5 mg to at least 40 mg, at least 0.5 mg to at least 30 mg, at least 1 mg to at least 30 mg, at least 5 mg to at least 30 mg, at least 0.5 mg to at least 20 mg, at least 1 mg to at least 20 mg, at least 2 mg to at least 20 mg, at least 5 mg to at least 20 mg, at least 0.5 mg to at least 15 mg, at least 1 mg to at least 15 mg, at least 2 mg to at least 15 mg, at least 3 mg to at least 15 mg, at least 5 mg to at least 15 mg, at least 0.5 mg to at least 10 mg, at least 1 mg to at least 10 mg, or at least 5 mg to at least 10 mg once per week.

**[0649]** In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is administered at a dose of at least about 0.5 mg to at least about 50 mg once per week. In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is administered at a dose of at least about 0.5 mg to at least about 50 mg, at least about 1 mg to at least about 50 mg, at least about 5 mg to at least about 50 mg, at least about 0.5 mg to at least about 40 mg, at least about 1 mg to at least about 40 mg, at least about 5 mg to at least about 40 mg, at least about 0.5 mg to at least about 30 mg, at least about 1 mg to at least about 30 mg, at least about 5 mg to at least about 30 mg, at least about 0.5 mg to at least about 20 mg, at least about 1 mg to at least about 20 mg, at least about 2 mg to at least about 20 mg, at least about 5 mg to at least about 20 mg, at least about 0.5 mg to at least about 15 mg, at least about 1 mg to at least about 15 mg, at least about 2 mg to at least about 15 mg, at least about 3 mg to at least about 15 mg, at least about 5 mg to at least about 15 mg, at least about 0.5 mg to at least about 10 mg, at least about 1 mg to at least about 10 mg, or at least about 5 mg to at least about 10 mg once per week.

**[0650]** In some embodiments, the weight loss agent is mazdutide and is administered at a dose of about 0.5 mg to about 50 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of about 0.5 mg to about 50 mg, about 1 mg to about 50 mg, about 5 mg to about 50 mg, about 0.5 mg to about 40 mg, about 1 mg to about 40 mg, about 5 mg to about 40 mg, about 0.5 mg to about 30 mg, about 1 mg to about 30 mg, about 5 mg to about 30 mg, about 0.5 mg to about 20 mg, about 1 mg to about 20 mg, about 2 mg to about 20 mg, about 5 mg to about 20 mg, about 0.5 mg to about 15 mg, about 1 mg to about 15 mg, about 2 mg to about 15 mg, about 3 mg to about 15 mg, about 5 mg to about 15 mg, about 0.5 mg to about 10 mg, about 1 mg to about 10 mg, or about 5 mg to about 10 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of less than about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg once per week.

**[0651]** In some embodiments, the weight loss agent is mazdutide and is administered at a dose of at least 0.5 mg to at least 50 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of at least 0.5 mg to at least 50 mg, at least 1 mg to at least 50 mg, at least 5 mg to at least 50 mg, at least 0.5 mg to at least 40 mg, at least 1 mg to at least 40 mg, at least 5 mg to at least 40 mg, at least 0.5 mg to at least 30 mg, at least 1 mg to at least 30 mg, at least 5 mg to at least 30 mg, at least 0.5 mg to at least 20 mg, at least 1 mg to at least 20 mg, at least 2 mg to at least 20 mg, at least 5 mg to at least 20 mg, at least 0.5 mg to at least 15 mg, at least 1 mg to at least 15 mg, at least 2 mg to at least 15 mg, at least 3 mg to at least 15 mg, at least 5 mg to at least 15 mg, at least 0.5 mg to at least 10 mg, at least 1 mg to at least 10 mg, or at least 5 mg to at least 10 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of at least 5 mg, at least 6 mg, at least 7 mg, at least 8 mg, at least 9 mg, or at least 10 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of less than at least 5 mg, at least 6 mg, at least 7 mg, at least 8 mg, at least 9 mg, or at least 10 mg once per week.

**[0652]** In some embodiments, the weight loss agent is mazdutide and is administered at a dose of at least about 0.5 mg to at least about 50 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of at least about 0.5 mg to at least about 50 mg, at least about 1 mg to at least about 50 mg, at least about 5 mg to at least about 50 mg, at least about 0.5 mg to at least about 40 mg, at least about 1 mg to at least about 40 mg, at least about 5 mg to at least about 40 mg, at least about 0.5 mg to at least about 30 mg, at least about 1 mg to at least about 30 mg, at least about 5 mg to at least about 30 mg, at least about 0.5 mg to at least about 20 mg, at least about 1 mg to at least about 20 mg, at least about 2 mg to at least about 20 mg, at least about 5 mg to at least about 20 mg, at least about 0.5 mg to at least about 15 mg, at least about 1 mg to at least about 15 mg, at least about 2 mg to at least about 15 mg, at least about 3 mg to at least about 15 mg, at least about 5 mg to at least about 15 mg, at least about 0.5 mg to at least about 10 mg, at least about 1 mg to at least about 10 mg, or at least about 5 mg to at least about 10 mg once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of at least about 5 mg, at least about 6 mg, at least about 7 mg, at least about 8 mg, at least about 9 mg, or at least about 10 mg

once per week. In some embodiments, the weight loss agent is mazdutide and is administered at a dose of less than at least about 5 mg, at least about 6 mg, at least about 7 mg, at least about 8 mg, at least about 9 mg, or at least about 10 mg once per week.

**[0653]** In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist and is administered at a dose of about 0.05 mg to about 50 mg once per week. In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist and is administered at a dose of about 0.05 mg to about 50 mg, about 0.5 mg to about 50 mg, about 1 mg to about 50 mg, about 5 mg to about 50 mg, about 0.5 mg to about 40 mg, about 1 mg to about 40 mg, about 5 mg to about 40 mg, about 0.5 mg to about 30 mg, about 1 mg to about 30 mg, about 5 mg to about 30 mg, about 0.5 mg to about 20 mg, about 1 mg to about 20 mg, about 2 mg to about 20 mg, about 5 mg to about 20 mg, about 0.5 mg to about 15 mg, about 1 mg to about 15 mg, about 2 mg to about 15 mg, about 3 mg to about 15 mg, about 5 mg to about 15 mg, about 0.5 mg to about 10 mg, about 1 mg to about 10 mg, or about 5 mg to about 10 mg once per week.

**[0654]** In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist and is administered at a dose of at least 0.05 mg to at least 50 mg once per week. In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist and is administered at a dose of at least 0.05 mg to at least 50 mg, at least 0.5 mg to at least 50 mg, at least 1 mg to at least 50 mg, at least 5 mg to at least 50 mg, at least 0.5 mg to at least 40 mg, at least 1 mg to at least 40 mg, at least 5 mg to at least 40 mg, at least 0.5 mg to at least 30 mg, at least 1 mg to at least 30 mg, at least 5 mg to at least 30 mg, at least 0.5 mg to at least 20 mg, at least 1 mg to at least 20 mg, at least 2 mg to at least 20 mg, at least 5 mg to at least 20 mg, at least 0.5 mg to at least 15 mg, at least 1 mg to at least 15 mg, at least 2 mg to at least 15 mg, at least 3 mg to at least 15 mg, at least 5 mg to at least 15 mg, at least 0.5 mg to at least 10 mg, at least 1 mg to at least 10 mg, or at least 5 mg to at least 10 mg once per week.

**[0655]** In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist and is administered at a dose of at least about 0.05 mg to at least about 50 mg once per week. In some embodiments, the weight loss agent is a GLP-1/GIP/glucagon receptor trifunctional agonist and is administered at a dose of at least about



0.05 mg to at least about 50 mg, at least about 0.5 mg to at least about 50 mg, at least about 1 mg to at least about 50 mg, at least about 5 mg to at least about 50 mg, at least about 0.5 mg to at least about 40 mg, at least about 1 mg to at least about 40 mg, at least about 5 mg to at least about 40 mg, at least about 0.5 mg to at least about 30 mg, at least about 1 mg to at least about 30 mg, at least about 5 mg to at least about 30 mg, at least about 0.5 mg to at least about 20 mg, at least about 1 mg to at least about 20 mg, at least about 2 mg to at least about 20 mg, at least about 5 mg to at least about 20 mg, at least about 0.5 mg to at least about 15 mg, at least about 1 mg to at least about 15 mg, at least about 2 mg to at least about 15 mg, at least about 3 mg to at least about 15 mg, at least about 5 mg to at least about 15 mg, at least about 0.5 mg to at least about 10 mg, at least about 1 mg to at least about 10 mg, or at least about 5 mg to at least about 10 mg once per week.

**[0656]** In some embodiments, the weight loss agent is retatrutide and is administered at a dose of about 0.5 mg to about 50 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of about 0.5 mg to about 50 mg, about 1 mg to about 50 mg, about 5 mg to about 50 mg, about 0.5 mg to about 40 mg, about 1 mg to about 40 mg, about 5 mg to about 40 mg, about 0.5 mg to about 30 mg, about 1 mg to about 30 mg, about 5 mg to about 30 mg, about 0.5 mg to about 20 mg, about 1 mg to about 20 mg, about 2 mg to about 20 mg, about 5 mg to about 20 mg, about 0.5 mg to about 15 mg, about 1 mg to about 15 mg, about 2 mg to about 15 mg, about 3 mg to about 15 mg, about 5 mg to about 15 mg, about 0.5 mg to about 10 mg, about 1 mg to about 10 mg, or about 5 mg to about 10 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of about 0.5 mg, about 1.5 mg, about 3 mg, about 6 mg, about 9 mg, or about 12 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of less than about 0.5 mg, about 1.5 mg, about 3 mg, about 6 mg, about 9 mg, or about 12 mg once per week.

**[0657]** In some embodiments, the weight loss agent is retatrutide and is administered at a dose of at least 0.5 mg to at least 50 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of at least 0.5 mg to at least 50 mg, at least 1 mg to at least 50 mg, at least 5 mg to at least 50 mg, at least 0.5 mg to at least 40 mg, at least 1 mg to at least 40 mg, at least 5 mg to at least 40 mg, at least 0.5 mg

to at least 30 mg, at least 1 mg to at least 30 mg, at least 5 mg to at least 30 mg, at least 0.5 mg to at least 20 mg, at least 1 mg to at least 20 mg, at least 2 mg to at least 20 mg, at least 5 mg to at least 20 mg, at least 0.5 mg to at least 15 mg, at least 1 mg to at least 15 mg, at least 2 mg to at least 15 mg, at least 3 mg to at least 15 mg, at least 5 mg to at least 15 mg, at least 0.5 mg to at least 10 mg, at least 1 mg to at least 10 mg, or at least 5 mg to at least 10 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of at least 0.5 mg, at least 1.5 mg, at least 3 mg, at least 6 mg, at least 9 mg, or at least 12 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of less than at least 0.5 mg, at least 1.5 mg, at least 3 mg, at least 6 mg, at least 9 mg, or at least 12 mg once per week.

**[0658]** In some embodiments, the weight loss agent is retatrutide and is administered at a dose of at least about 0.5 mg to at least about 50 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of at least about 0.5 mg to at least about 50 mg, at least about 1 mg to at least about 50 mg, at least about 5 mg to at least about 50 mg, at least about 0.5 mg to at least about 40 mg, at least about 1 mg to at least about 40 mg, at least about 5 mg to at least about 40 mg, at least about 0.5 mg to at least about 30 mg, at least about 1 mg to at least about 30 mg, at least about 5 mg to at least about 30 mg, at least about 0.5 mg to at least about 20 mg, at least about 1 mg to at least about 20 mg, at least about 2 mg to at least about 20 mg, at least about 5 mg to at least about 20 mg, at least about 0.5 mg to at least about 15 mg, at least about 1 mg to at least about 15 mg, at least about 2 mg to at least about 15 mg, at least about 3 mg to at least about 15 mg, at least about 5 mg to at least about 15 mg, at least about 0.5 mg to at least about 10 mg, at least about 1 mg to at least about 10 mg, or at least about 5 mg to at least about 10 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of at least about 0.5 mg, at least about 1.5 mg, at least about 3 mg, at least about 6 mg, at least about 9 mg, or at least about 12 mg once per week. In some embodiments, the weight loss agent is retatrutide and is administered at a dose of less than at least about 0.5 mg, at least about 1.5 mg, at least about 3 mg, at least about 6 mg, at least about 9 mg, or at least about 12 mg once per week.

**[0659]** In some embodiments, the weight loss agent is a MC4 receptor agonist and is administered at a dose ranging from about 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 mg to about 20 mg, or about 7.5 mg to about 15 mg once daily. In some embodiments, the weight loss agent is a MC4 receptor agonist and is administered at a dose of about 10 mg once daily.

**[0660]** In some embodiments, the weight loss agent is a MC4 receptor agonist and is administered at a dose ranging from at least 0.5 mg to at least 50 mg, at least 1 mg to at least 40 mg, at least 2.5 mg to at least 30 mg, at least 5 mg to at least 20 mg, or at least 7.5 mg to at least 15 mg once daily. In some embodiments, the weight loss agent is a MC4 receptor agonist and is administered at a dose of at least 10 mg once daily.

**[0661]** In some embodiments, the weight loss agent is a MC4 receptor agonist and is administered at a dose ranging from at least about 0.5 mg to at least about 50 mg, at least about 1 mg to at least about 40 mg, at least about 2.5 mg to at least about 30 mg, at least about 5 mg to at least about 20 mg, or at least about 7.5 mg to at least about 15 mg once daily. In some embodiments, the weight loss agent is a MC4 receptor agonist and is administered at a dose of at least about 10 mg once daily.

**[0662]** In some embodiments, the weight loss agent is setmelanotide and is administered at a dose ranging from about 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 mg to about 20 mg, or about 7.5 mg to about 15 mg once daily. In some embodiments, the weight loss agent is setmelanotide and is administered at a dose of about 10 mg once daily. In some embodiments, the weight loss agent is setmelanotide and is administered at a dose of less than about 10 mg once daily.

**[0663]** In some embodiments, the weight loss agent is setmelanotide and is administered at a dose ranging from at least 0.5 mg to at least 50 mg, at least 1 mg to at least 40 mg, at least 2.5 mg to at least 30 mg, at least 5 mg to at least 20 mg, or at least 7.5 mg to at least 15 mg once daily. In some embodiments, the weight loss agent is setmelanotide and is administered at a dose of at least 10 mg once daily. In some embodiments, the weight loss agent is setmelanotide and is administered at a dose of less than at least 10 mg once daily.

**[0664]** In some embodiments, the weight loss agent is setmelanotide and is administered at a dose ranging from at least about 0.5 mg to at least about 50 mg, at least about 1 mg to at least about 40 mg, at least about 2.5 mg to at least about 30 mg, at least about 5 mg to at least about 20 mg, or at least about 7.5 mg to at least about 15 mg once daily. In some embodiments, the weight loss agent is setmelanotide and is administered at a dose of at least about 10 mg once daily. In some embodiments, the weight loss agent is setmelanotide and is administered at a dose of less than at least about 10 mg once daily.

**[0665]** In some embodiments, the weight loss agent lmcivree® and is administered according to the label instructions. In some embodiments, the weight loss agent is lmcivree® and is administered less frequently and/or at a lower dose than specified on the label instructions.

**[0666]** In some embodiments, the weight loss agent is administered before a meal. In some embodiments, the weight loss agent is administered after a meal. In some embodiments, the weight loss agent is administered with a meal.

**[0667]** In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof (e.g., the second pharmaceutical composition) is administered hourly (such as every hour, every 2 hours, every 4 hours, every 8 hours, etc.), once a day, or twice a day. In some embodiments, the non-naturally occurring melanocortin analog is administered every morning, every evening, or every afternoon. In some embodiments, the non-naturally occurring melanocortin analog is administered before a meal, after a meal, or with a meal.

**[0668]** In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof may be administered as a dosing regimen comprising once, twice, or three times daily administration on a (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five week off; (vi) four weeks of therapy followed by one, two, three, four or five week off; (vii) five weeks of therapy followed by one, two, three, four or five week off; or (viii) monthly schedule. The (i)-(viii) schedules may be repeated 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times or more. In some embodiments, the non-naturally occurring melanocortin analog

or pharmaceutical composition thereof is administered at various dosages during the dosing regimen (e.g., a first dose with an effective amount of 10 mg/kg and a second dose with an effective amount of 5 mg/kg).

**[0669]** In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is administered once every other day, once every 2 or 3 days, once every third day, once per week, once every other week, once every third week, once every month, once every six weeks, once every other month, once every three months, once every six months, or once per year. Administration of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof at any of the dosing frequencies of the present technology may be repeated for a total of at least 2 dosages, at least 3 dosages, at least 4 dosages, at least 5 dosages, at least 10 dosages, at least 15 dosages, at least 20 dosages, at least 30 dosages, at least 40 dosages, at least 50 dosages or more. In some embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is the same during a treatment regimen. In other embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is different during a treatment regimen. The non-naturally occurring melanocortin analog or the pharmaceutical composition thereof may be administered even less frequently. Alternatively, the dosage regimen may be decreased or increased from an initial dosing regimen for days, weeks, months, or years. In some embodiments, the dosing regimen is repeated at other intervals.

#### Methods of Treatment

**[0670]** The present technology comprises methods of treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with metabolic dysfunction using a non-naturally occurring melanocortin analog alone or in combination with a weight loss agent of the present technology. The methods of the present technology may promote fat (e.g., epididymal fat or perirenal fat) loss, prevent muscle loss or maintain muscle mass, decrease body weight, accelerate weight loss, decrease fat mass to lean mass ratio, improve body composition and/or BMI, reduce waist circumference, prevent brain mass loss or maintain brain mass, or any combination thereof.

**[0671]** The present technology comprises methods of treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with use of a weight loss agent in a subject by administering a non-naturally occurring melanocortin analog to the subject alone or prior to, during, and/or after administration of the weight loss agent. The methods of the present technology may reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. The methods of the present technology may decrease the risk and/or incidence of adverse cardiovascular events associated with the use of a weight loss agent such as, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof. Methods of the present technology may also reduce hemoglobin A1c levels and/or regulate plasma insulin, and/or myocardial regeneration in a subject using a weight loss agent by maintaining or increasing lean mass in the subject. In some embodiments, the method decreases gastrointestinal effects such as, for example, nausea, vomiting, and diarrhea in the subject. In some embodiments, the method decreases inflammation in the subject. In some embodiments, the method preserves or improves kidney functions in the subject.

**[0672]** These methods may comprise administration of a non-naturally occurring melanocortin analog without administration of a weight loss agent. In some embodiments, the methods of the present technology include administration of a non-naturally occurring melanocortin analog to a subject in need thereof prior to, during, and/or after administration of a weight loss agent to the subject. The subject may have metabolic dysfunction or another condition other than metabolic dysfunction for which a therapeutic benefit is provided with administration of a weight loss agent. In some embodiments, the subject is overweight or obese. In some embodiments, the subject has glucose intolerance or diabetes mellitus. In some embodiments, the subject has inflammation, such as obesity-related inflammation.

**[0673]** In some aspects, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with metabolic dysfunction in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject without administration of a

weight loss agent or administration of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of the weight loss agent, wherein the one or more symptoms or conditions include weight gain, obesity glucose intolerance, and/or diabetes mellitus.

**[0674]** In some aspects, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with metabolic dysfunction in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject alone or prior to, during, and/or after administration of the weight loss agent, wherein the one or more symptoms or conditions include obesity-related inflammation, increased hemoglobin A1c levels, decreased kidney function or kidney injury, such as diabetic nephropathy, and/or insulin resistance. In some embodiments, the method comprises administering a non-naturally occurring melanocortin agonist to the subject alone or prior to, during, and/or after administration of the weight loss agent.

**[0675]** In some embodiments, the present technology comprises methods of preventing, reducing, or otherwise ameliorating weight gain in a subject after administration of a weight loss agent (e.g., after the completion of administration and/or a dosing regimen), comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent.

**[0676]** In some embodiments, the present technology comprises methods of preventing, reducing, or otherwise ameliorating fat mass gain in a subject after administration of a weight loss agent (e.g., after the completion of administration and/or a dosing regimen), comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent.

**[0677]** In some embodiments, the present technology comprises methods of preventing, reducing, or otherwise ameliorating blood sugar elevation in a subject after administration of a weight loss agent (e.g., after the completion of administration and/or a dosing regimen), comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent.

**[0678]** In some embodiments, the present technology comprises methods of preventing, reducing, or otherwise ameliorating brain mass loss in a subject after or during (e.g., coadministration or between doses of a weight loss agent) administration of a weight loss agent (e.g., after the completion of administration and/or a dosing regimen), comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent.

**[0679]** In some embodiments, the present technology comprises methods of preventing, reducing, or otherwise ameliorating muscle mass loss in a subject after or during (e.g., coadministration or between doses of a weight loss agent) administration of a weight loss agent (e.g., after the completion of administration and/or a dosing regimen), comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent.

**[0680]** In some embodiments, the present technology comprises methods of preventing, reducing, or otherwise ameliorating a sleep disorder in a subject comprising administering a non-naturally occurring melanocortin analog to the subject alone or prior to, during, and/or after administration of a weight loss agent of the present technology. In some embodiments, the sleep disorder is sleep apnea.

**[0681]** In some aspects, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with a weight loss agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent. In some embodiments, the one or more side effects associated with a weight loss agent is lean mass loss. In some embodiments, the method reduces lean mass loss, maintains lean mass, or promotes lean mass gain in the subject. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the one or more side effects associated with a weight loss agent is an adverse cardiovascular event such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any



combination thereof in the subject. In some embodiments, the method reduces the risk or incidence of adverse cardiovascular events in the subject. In some embodiments, the one or more side effects associated with a weight loss agent is a gastrointestinal effect such as nausea, vomiting, and diarrhea in the subject. In some embodiments, the method decreases the gastrointestinal effect of the weight loss agent on the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0682]** In some aspects, the present technology comprises a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of a weight loss agent, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-

380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0683]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of a GLP-1 receptor agonist, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0684]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of semaglutide, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments,

the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0685]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of Ozempic®, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0686]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of Wegovy®, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In

some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0687]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of Rybelsus®, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0688]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of exenatide, comprising administering a non-naturally occurring

melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0689]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of Byetta®, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0690]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of Bydureon®, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0691]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of dulaglutide, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the

non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0692]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of Trulicity®, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0693]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of orforglipron, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs:

223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0694]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of a dual GLP-1/GIP receptor agonist, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0695]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of tirzepatide, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In



some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0696]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of Mounjaro™, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0697]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after

administration of Zepbound™, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0698]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of GLP-1/glucagon receptor agonist, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and

378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0699]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of mazdutide, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0700]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of a trifunctional GLP-1/GIP/glucagon receptor agonist, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470,

474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0701]** In some embodiments, the method is a method of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject prior to, during, and/or after administration of retatrutide, comprising administering a non-naturally occurring melanocortin analog to the subject. In such method, the subject's lean mass may be maintained or increased while the overall mass of the subject is decreased. The lean mass may be lean muscle mass, such as skeletal muscle mass, cardiac muscle mass, or both. In some embodiments, the method improves body composition and/or BMI of the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0702]** Methods of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject may also treat, prevent, or reduce one or more side effects associated with the use of a weight loss agent. In some embodiments, the method further reduces the risk or incidence of adverse cardiovascular events, such as, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof, and/or decrease

gastrointestinal effects such as, nausea, vomiting, and diarrhea that are associated with use of the weight loss agent or the non-naturally occurring melanocortin analog. The methods may also treat, prevent, or reduce one or more side effects associated with the use of the non-naturally occurring melanocortin analog. For example, methods of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain may prevent or reduce the risk or incidence of adverse cardiovascular events associated with the use of a non-naturally occurring melanocortin agonist, such as sinus tachycardia. Additionally, such methods may reduce hemoglobin A1c levels, decrease inflammation, regulate plasma insulin and/or preserve or improve kidney function in the subject.

**[0703]** Methods of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in a subject comprising administering a non-naturally occurring melanocortin analog prior to, during, or after administration of the weight loss agent may comprise administering the weight loss agent at lower or less frequent dose relative to a dose of the weight loss agent administered without the non-naturally occurring melanocortin analog. The lower or less frequent dose of the weight loss agent may still achieve the desired effect, e.g., weight and/or fat mass loss, while preventing or reducing unwanted side effects, such as, for example, adverse cardiovascular events and gastrointestinal effects.

**[0704]** In some embodiments, the weight loss agent is a GLP-1 receptor agonist and is administered at a lower or less frequent dose relative to a dose of the GLP-1 receptor agonist administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is semaglutide and is administered at a lower or less frequent dose relative to a dose of semaglutide administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Ozempic® and is administered at a lower or less frequent dose relative to a dose of Ozempic® administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Wegovy® and is administered at a lower or less frequent dose relative to a dose of Wegovy® administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Rybelsus® and is administered at a lower or less frequent dose relative to a dose of Rybelsus® administered without the non-naturally occurring melanocortin analog. In some

embodiments, the weight loss agent is exenatide and is administered at a lower or less frequent dose relative to a dose of exenatide administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Byetta® and is administered at a lower or less frequent dose relative to a dose of Byetta® administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Bydureon® and is administered at a lower or less frequent dose relative to a dose of Bydureon® administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is dulaglutide and is administered at a lower or less frequent dose relative to a dose of dulaglutide administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Trulicity® and is administered at a lower or less frequent dose relative to a dose of Trulicity® administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is orforglipron and is administered at a lower or less frequent dose relative to a dose of orforglipron administered without the non-naturally occurring melanocortin analog.

**[0705]** In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist and is administered at a lower or less frequent dose relative to a dose of the dual GLP-1/GIP receptor agonist administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is tirzepatide and is administered at a lower or less frequent dose relative to a dose of tirzepatide administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Mounjaro™ and is administered at a lower or less frequent dose relative to a dose of Mounjaro™ administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is Zepbound™ and is administered at a lower or less frequent dose relative to a dose of Zepbound™ administered without the non-naturally occurring melanocortin analog.

**[0706]** In some embodiments, the weight loss agent is a GLP-1/glucagon receptor coagonist and is administered at a lower or less frequent dose relative to a dose of the GLP-1/glucagon receptor coagonist administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is mazdutide and is

administered at a lower or less frequent dose relative to a dose of mazdutide administered without the non-naturally occurring melanocortin analog.

**[0707]** In some embodiments, the weight loss agent is a trifunctional GLP-1/GIP/glucagon receptor agonist and is administered at a lower or less frequent dose relative to a dose of the trifunctional GLP-1/GIP/glucagon receptor agonist administered without the non-naturally occurring melanocortin analog. In some embodiments, the weight loss agent is retatrutide and is administered at a lower or less frequent dose relative to a dose of retatrutide administered without the non-naturally occurring melanocortin analog.

**[0708]** In some aspects, the present technology comprises a method of reducing body weight and/or fat mass in a subject in need thereof, comprising administering to the subject (a) a weight loss agent and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the weight loss agent. In some embodiments, the non-naturally occurring melanocortin analog is administered after the weight loss agent. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of the weight loss agent. For example, the subject may not have lost any weight with the weight loss agent or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the weight loss agent, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the weight loss agent, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and

498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0709]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) a GLP-1 receptor agonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the GLP-1 receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered after the GLP-1 receptor agonist. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of the GLP-1 receptor agonist. For example, the subject may not have lost any weight with the GLP-1 receptor agonist, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the GLP-1 receptor agonist, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the GLP-1 receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments,



the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0710]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) semaglutide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. In some embodiments, administration of a combination of semaglutide and a non-naturally occurring melanocortin analog produces an additive effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of semaglutide. In some embodiments, the non-naturally occurring melanocortin analog is administered after semaglutide. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of semaglutide. For example, the subject may not have lost any weight with semaglutide, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of semaglutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to semaglutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297,

363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0711]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Ozempic® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Ozempic®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Ozempic®. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Ozempic®. For example, the subject may not have lost any weight with Ozempic®, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Ozempic®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Ozempic®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs:

223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0712]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Wegovy® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Wegovy®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Wegovy®. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Wegovy®. For example, the subject may not have lost any weight with Wegovy®, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Wegovy®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Wegovy®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-

485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0713]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Rybelsus® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Rybelsus®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Rybelsus®. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Rybelsus®. For example, the subject may not have lost any weight with Rybelsus®, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Rybelsus®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Rybelsus®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the

non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0714]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) exenatide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of exenatide. In some embodiments, the non-naturally occurring melanocortin analog is administered after exenatide. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of exenatide. For example, the subject may not have lost any weight with exenatide, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of exenatide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to exenatide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some

embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0715]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Byetta® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Byetta®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Byetta®. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Byetta®. For example, the subject may not have lost any weight with Byetta®, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Byetta®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Byetta®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0716]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Bydureon® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Bydureon®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Bydureon®. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Bydureon®. For example, the subject may not have lost any weight with Bydureon®, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Bydureon®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Bydureon®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0717]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) dulaglutide and (b) a

non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of dulaglutide. In some embodiments, the non-naturally occurring melanocortin analog is administered after dulaglutide. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of dulaglutide. For example, the subject may not have lost any weight with dulaglutide, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of dulaglutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to dulaglutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0718]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Trulicity® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog



may be administered prior to, during, and/or after administration of Trulicity®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Trulicity®. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Trulicity®. For example, the subject may not have lost any weight with Trulicity®, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Trulicity®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Trulicity®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0719]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) orforglipron and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of orforglipron. In some embodiments, the non-naturally occurring melanocortin analog is administered after

orforglipron. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of orforglipron. For example, the subject may not have lost any weight with orforglipron, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of orforglipron, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to orforglipron, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. v.

**[0720]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) a dual GLP-1/GIP receptor agonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the dual GLP-1/GIP receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered after the dual GLP-1/GIP receptor agonist. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of the dual GLP-1/GIP receptor agonist. For example, the subject may not have lost any weight with the dual GLP-1/GIP receptor agonist, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the dual GLP-1/GIP receptor agonist, and

administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the dual GLP-1/GIP receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0721]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) tirzepatide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. In some embodiments, administration of a combination of tirzepatide and a non-naturally occurring melanocortin analog produces a synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of tirzepatide. In some embodiments, the non-naturally occurring melanocortin analog is administered after tirzepatide. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of tirzepatide. For example, the subject may not have lost any weight with tirzepatide, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is

administered prior to administration of tirzepatide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to tirzepatide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0722]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Mounjaro™ and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Mounjaro™. In some embodiments, the non-naturally occurring melanocortin analog is administered after Mounjaro™. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Mounjaro™. For example, the subject may not have lost any weight with Mounjaro™, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Mounjaro™, and administration of the non-naturally occurring melanocortin analog makes

the subject more responsive to Mounjaro™, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0723]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) Zepbound™ and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Zepbound™. In some embodiments, the non-naturally occurring melanocortin analog is administered after Zepbound™. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of Zepbound™. For example, the subject may not have lost any weight with Zepbound™, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Zepbound™, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Zepbound™, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce

lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0724]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) a GLP-1/glucagon receptor coagonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the GLP-1/glucagon receptor coagonist. In some embodiments, the non-naturally occurring melanocortin analog is administered after the GLP-1/glucagon receptor coagonist. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of the GLP-1/glucagon receptor coagonist. For example, the subject may not have lost any weight with the GLP-1/glucagon receptor coagonist, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the GLP-1/glucagon receptor coagonist, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the GLP-1/glucagon receptor coagonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may

also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0725]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) mazdutide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of mazdutide. In some embodiments, the non-naturally occurring melanocortin analog is administered after mazdutide. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of mazdutide. For example, the subject may not have lost any weight with mazdutide, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of mazdutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to mazdutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose

intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0726]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) a trifunctional GLP-1/GIP/glucagon receptor agonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the trifunctional GLP-1/GIP/glucagon receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered after the trifunctional GLP-1/GIP/glucagon receptor agonist. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of the trifunctional GLP-1/GIP/glucagon receptor agonist. For example, the subject may not have lost any weight with the trifunctional GLP-1/GIP/glucagon receptor agonist, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the trifunctional GLP-1/GIP/glucagon receptor agonist, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the trifunctional GLP-1/GIP/glucagon receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or



promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0727]** In some embodiments, the method of reducing body weight and/or fat mass in a subject in need thereof comprises administering to the subject (a) retatrutide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of retatrutide. In some embodiments, the non-naturally occurring melanocortin analog is administered after retatrutide. In some embodiments, the subject failed to lose sufficient fat mass and/or body weight following administration of retatrutide. For example, the subject may not have lost any weight with retatrutide, or the subject may have lost weight initially and then, after a period of time, hit a plateau with body weight and/or fat mass loss such that the subject did not lose the desired amount of body weight and/or fat mass. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of retatrutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to retatrutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also treat, prevent, or reduce glucose

intolerance and/or diabetes mellitus in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0728]**

**[0729]** Methods of reducing body weight and/or fat mass of the present technology may also treat, prevent, or reduce one or more side effects associated with the use of the weight loss agent. In some embodiments, the method further reduces the risk or incidence of adverse cardiovascular events, such as, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof, and/or decreases gastrointestinal effects such as, nausea, vomiting, and diarrhea that are associated with use of the weight loss agent or the non-naturally occurring melanocortin analog. The methods may also treat, prevent, or reduce one or more side effects associated with the use of the non-naturally occurring melanocortin analog. For example, methods of reducing body weight and/or fat mass may prevent or reduce the risk or incidence of adverse cardiovascular events associated with the use of a non-naturally melanocortin agonist, such as sinus tachycardia. Additionally, such methods may reduce hemoglobin A1c levels, decrease obesity-related inflammation, regulate plasma insulin and/or preserve or improve kidney function in the subject.

**[0730]** In some aspects, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus

in a subject in need thereof, comprising administering to the subject (a) a weight loss agent and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the weight loss agent. In some embodiments, the non-naturally occurring melanocortin analog is administered after the weight loss agent. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of the weight loss agent. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the weight loss agent, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the weight loss agent, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0731]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) a GLP-1 receptor agonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring

melanocortin analog may be administered prior to, during, and/or after administration of the GLP-1 receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered after the GLP-1 receptor agonist. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of the GLP-1 receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the GLP-1 receptor agonist, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the GLP-1 receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0732]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) semaglutide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of semaglutide. In some embodiments, the non-naturally occurring melanocortin analog is administered after semaglutide. In some embodiments, the subject did not exhibit sufficient glucose tolerance

following administration of semaglutide. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of semaglutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to semaglutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0733]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) Ozempic® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Ozempic®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Ozempic®. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Ozempic®. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Ozempic®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Ozempic®, compared to a subject who has not been administered the non-naturally

occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0734]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) Wegovy® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Wegovy®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Wegovy®. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Wegovy®. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Wegovy®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Wegovy®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a

sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0735]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) Rybelsus® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Rybelsus®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Rybelsus®. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Rybelsus®. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Rybelsus®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Rybelsus®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418,

464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0736]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) exenatide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of exenatide. In some embodiments, the non-naturally occurring melanocortin analog is administered after exenatide. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of exenatide. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of exenatide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to exenatide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs:



268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0737]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) Byetta® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Byetta®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Byetta®. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Byetta®. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Byetta®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Byetta®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0738]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need

thereof comprises administering to the subject (a) Bydureon® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Bydureon®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Bydureon®. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Bydureon®. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Bydureon®, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Bydureon®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0739]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) dulaglutide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of dulaglutide. In

some embodiments, the non-naturally occurring melanocortin analog is administered after dulaglutide. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of dulaglutide. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of dulaglutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to dulaglutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0740]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) Trulicity® and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Trulicity®. In some embodiments, the non-naturally occurring melanocortin analog is administered after Trulicity®. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Trulicity®. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Trulicity®, and administration

of the non-naturally occurring melanocortin analog makes the subject more responsive to Trulicity®, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0741]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) orforglipron and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of orforglipron. In some embodiments, the non-naturally occurring melanocortin analog is administered after orforglipron. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of orforglipron. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of orforglipron, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to orforglipron, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass

in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0742]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) a dual GLP-1/GIP receptor agonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the dual GLP-1/GIP receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered after the dual GLP-1/GIP receptor agonist. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of the dual GLP-1/GIP receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the dual GLP-1/GIP receptor agonist, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the dual GLP-1/GIP receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223,

228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0743]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) tirzepatide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of tirzepatide. In some embodiments, the non-naturally occurring melanocortin analog is administered after tirzepatide. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of tirzepatide. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of tirzepatide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to tirzepatide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some

embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0744]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) Mounjaro™ and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Mounjaro™. In some embodiments, the non-naturally occurring melanocortin analog is administered after Mounjaro™. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Mounjaro™. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Mounjaro™, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Mounjaro™, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-

naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0745]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) Zepbound™ and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of Zepbound™. In some embodiments, the non-naturally occurring melanocortin analog is administered after Zepbound™. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of Zepbound™. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of Zepbound™, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to Zepbound™, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.



**[0746]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) a GLP-1/glucagon receptor coagonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the GLP-1/glucagon receptor coagonist. In some embodiments, the non-naturally occurring melanocortin analog is administered after the GLP-1/glucagon receptor coagonist. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of the GLP-1/glucagon receptor coagonist. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the GLP-1/glucagon receptor coagonist, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the GLP-1/glucagon receptor coagonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0747]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) mazdutide and (b) a non-naturally

occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of mazdutide. In some embodiments, the non-naturally occurring melanocortin analog is administered after mazdutide. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of mazdutide. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of mazdutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to mazdutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0748]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) a trifunctional GLP-1/GIP/glucagon receptor agonist and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of the trifunctional GLP-1/GIP/glucagon receptor agonist. In

some embodiments, the non-naturally occurring melanocortin analog is administered after the trifunctional GLP-1/GIP/glucagon receptor agonist. In some embodiments, the subject did not exhibit sufficient glucose tolerance following administration of the trifunctional GLP-1/GIP/glucagon receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of the trifunctional GLP-1/GIP/glucagon receptor agonist, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the trifunctional GLP-1/GIP/glucagon receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0749]** In some embodiments, the method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof comprises administering to the subject (a) retatrutide and (b) a non-naturally occurring melanocortin analog to produce an additive or synergistic effect on glucose intolerance and/or diabetes mellitus in the subject. The non-naturally occurring melanocortin analog may be administered prior to, during, and/or after administration of retatrutide. In some embodiments, the non-naturally occurring melanocortin analog is administered after retatrutide. In some embodiments, the subject did not exhibit sufficient glucose tolerance

following administration of retatrutide. In some embodiments, the non-naturally occurring melanocortin analog is administered prior to administration of retatrutide, and administration of the non-naturally occurring melanocortin analog makes the subject more responsive to retatrutide, compared to a subject who has not been administered the non-naturally occurring melanocortin analog. The method may also reduce lean mass loss, maintain lean mass, or promote lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. The method may also reduce body weight and/or fat mass in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0750]** Methods of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject may also treat, prevent, or reduce one or more side effects associated with the use of the weight loss agent. In some embodiments, the method further reduces the risk or incidence of adverse cardiovascular events, such as, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof, and/or decrease gastrointestinal effects such as, nausea, vomiting, and diarrhea that are associated with use of the weight loss agent. The methods may also treat, prevent, or reduce one or more side effects associated with the use of the non-naturally occurring melanocortin analog. For example, methods of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus may prevent or reduce the risk or

incidence of adverse cardiovascular events associated with the use of a non-naturally melanocortin agonist, such as sinus tachycardia. Additionally, such methods may reduce hemoglobin A1c levels, decrease inflammation, regulate plasma insulin and/or preserve or improve kidney function in the subject.

**[0751]** In some embodiments, methods of promoting weight loss in a subject currently undergoing treatment with a weight loss agent in an amount sufficient to induce weight loss, comprise administering a non-naturally occurring melanocortin analog as of the present technology to the subject, wherein, prior to administration of the non-naturally occurring melanocortin analog, the subject failed to lose sufficient weight following administration of the weight loss agent. The method may also reduce the risk or incidence of adverse cardiovascular events, such as, for example, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof; decrease gastrointestinal effects such as, for example, nausea, vomiting, and diarrhea; decrease inflammation; and/or preserve or improve kidney function in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0752]** In some embodiments, methods of reducing fat mass in a subject currently undergoing treatment with a weight loss agent at an amount sufficient to induce weight loss, comprise administering a non-naturally occurring melanocortin analog to the subject,

wherein, prior to administration of the non-naturally occurring melanocortin analog, the subject failed to lose sufficient fat mass following administration of the weight loss agent. The method may also reduce the risk or incidence of adverse cardiovascular events, such as, for example, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof; decrease gastrointestinal effects such as, for example, nausea, vomiting, and diarrhea; decrease inflammation; and/or preserve or improve kidney function in the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(ID). In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0753]** In some aspects, methods of promoting weight loss in a subject prior to, during, and/or after administration of a weight loss agent, comprise administering a non-naturally occurring melanocortin analog to the subject, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject. The lean mass may be lean muscle mass such as skeletal muscle, cardiac muscle, or both. The method may also reduce the risk or incidence of adverse cardiovascular events, such as, for example, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof; decrease gastrointestinal effects such as, for example, nausea, vomiting, and diarrhea; decrease obesity-related

inflammation; and/or preserve or improve kidney function in the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0754]** In some embodiments, the method of promoting weight loss in a subject currently being administered a GLP-1 receptor agonist, the method comprising administering to the subject a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 3, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[0755]** In some aspects, methods of reducing fat mass in a subject prior to, during, and/or after administration of a weight loss agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the fat mass of the subject is reduced while lean muscle mass is maintained or increased or the loss of lean mass is reduced. The lean mass may be lean muscle mass such as skeletal muscle, cardiac muscle, or both. The method may also reduce the risk or incidence of adverse cardiovascular events, such as, for example, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof; decrease gastrointestinal effects such as, for example, nausea, vomiting, and diarrhea; decrease inflammation; and/or preserve or improve kidney function in the subject. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs:

223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 268 and 378-380. In some embodiments, the non-naturally occurring analog is any one of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[0756]** In some embodiments of the methods of the present technology, the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in body weight about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0757]** In some embodiments of the methods of the present technology, the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, or about a 30% reduction in fat mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0758]** In some embodiments of the methods of the present technology, the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0759]** In some embodiments of the method of the present technology, the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% increase in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0760]** In other aspects, the present technology comprises a method of suppressing appetite in a subject in need thereof, comprising administering a non-naturally occurring



melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent. Administration of the non-naturally occurring melanocortin analog prior to, during, and/or after administration of the weight loss agent may produce an additive or synergistic effect on suppressing the subject's appetite. In some embodiments, the weight loss agent is a GLP-1 receptor agonist and the non-naturally occurring melanocortin analog is a melanocortin agonist and administration of the combination therapy produces an additive effect on suppressing the subject's appetite. In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist and the non-naturally occurring melanocortin analog is a melanocortin agonist and administration of the combination therapy produces a synergistic effect on suppressing the subject's appetite.

**[0761]** In some embodiments, the method reduces cumulative food intake of the subject. Administration of the non-naturally occurring melanocortin analog prior to, during, and/or after administration of the weight loss agent may produce an additive or synergistic effect on reducing the subject's food intake. In some embodiments, the method reduces fat body mass and/or body weight of the subject.

**[0762]** In some embodiments, the subject exhibits about a 5%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, about a 30%, about a 35%, about a 40%, about a 45%, about a 50%, about a 60%, or about a 70% reduction in food intake per day about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0763]** In some embodiments of the methods of the present technology, the blood glucose level of the subject is decreased following administration of the combination therapy. In some embodiments, the blood glucose level of the subject is decreased following administration of a first dose of the combination therapy.

**[0764]** In some embodiments, the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in blood glucose level about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[0765]** In some embodiments, the methods of the present technology increase the efficacy of the weight loss agent relative to a control.

**[0766]** In some embodiments, the methods of the present technology prevent or reduce a weight increase following a weight loss, relative to a control. In some embodiments, the weight loss is a weight loss experienced after administration GLP-1 receptor agonist.

**[0767]** In some embodiments, the methods of the present technology prevent, reduce, or otherwise ameliorate a reduction in efficacy and/or an efficacy plateau (e.g., plateau in body weight and/or fat mass loss) of the weight loss agent relative to a control.

**[0768]** In some embodiments, the methods of the present technology reduce a blood sugar level in the subject, relative to a control.

**[0769]** In some embodiments, administration of the non-naturally occurring melanocortin analog results in a steadier and/or more consistent weight loss relative to administration the GLP-1 receptor agonist. In some embodiments, administration of the non-naturally occurring melanocortin analog results in a less tachyphylactic weight loss relative to administration the GLP-1 receptor agonist.

**[0770]** In some embodiments, administration of the non-naturally occurring melanocortin analog and the weight loss agent (simultaneously or sequentially) results in increased weight and/or fat mass loss relative to administration of the weight loss agent alone. In some embodiments, administration of the non-naturally occurring melanocortin analog and the weight loss agent (simultaneously or sequentially) results in increased weight and/or fat mass loss while maintaining lean mass relative to administration of the weight loss agent alone.

*Additional Benefits Over GLP-1 Receptor Agonist Monotherapies*

**[0771]** The non-naturally occurring melanocortin analogs of the present technology may solve or improve shortcomings observed with administration of GLP-1 receptor agonist monotherapies. In some embodiments, the GLP-1 receptor agonist is semaglutide or tirzepatide. For example, the non-naturally occurring melanocortin analogs of the present technology may serve as a GLP-1 receptor agonist alternative or may counteract unwanted outcomes resulting from administration of a GLP-1 receptor agonist when the non-naturally

occurring melanocortin analog is administered alone (e.g., as a monotherapy or before or after administration of a GLP-1 receptor agonist) or in combination with a GLP-1 receptor agonist (e.g., before administration of the GLP-1 receptor agonist, after administration of the GLP-1 receptor agonist, or concurrently with administration of the GLP-1 receptor agonist). For example, the non-naturally occurring melanocortin analogs may improve one or more of tolerance (e.g., a reduction in nausea), muscle retention, patient preference and/or compliance relative to administration of a GLP-1 receptor agonist alone or otherwise without the non-naturally occurring melanocortin analog. Administration of the GLP-1 receptor agonist alone \*i.e., GLP-1 receptor agonist monotherapy) refers to administration without the non-naturally occurring melanocortin analog of the present technology. Administration of the GLP-1 receptor agonist alone may comprise administration with one or more compounds that are not the non-naturally occurring melanocortin analogs of the present technology.

**[0772]** Without intending to be limiting, the improved tolerance may be attributed to lower dosages of the GLP-1 receptor agonist when administered in combination with the non-naturally occurring melanocortin analog compared to higher dosage of the GLP-1 receptor agonists administered alone without the non-naturally occurring melanocortin analogs. Non-limiting examples of improved tolerance include reduced nausea, improved muscle retention, and improved patient compliance. In some embodiments, the GLP-1 receptor agonist administered in combination with the non-naturally occurring melanocortin analog is administered at a dose that is about 5% or less, about 10% or less, about 15% or less, about 20% or less, about 30% or less, about 35% or less, about 40% or less, about 45% or less, about 50% or less, about 55% or less, 60% or less, about 65% or less, about 70% or less, or about 75% or less of the dose of the GLP-1 receptor agonist administered alone without the non-naturally occurring melanocortin analogs.

**[0773]** In some embodiments, the non-naturally occurring melanocortin analogs may improve tolerance of a GLP-1 receptor agonist, relative to administration of a GLP-1 receptor agonist alone or otherwise without the non-naturally occurring melanocortin analog. The improved tolerance may comprise a reduction in nausea compared to administration of a GLP-1 receptor agonist alone.

**[0774]** In some embodiments, the non-naturally occurring melanocortin analogs may improve a muscle retention level relative to administration of a GLP-1 receptor agonist alone or otherwise without the non-naturally occurring melanocortin analog. The improved muscle retention may comprise a reduced muscle mass loss, an increase in muscle mass gain, or an increase in muscle mass maintenance, relative to administration of a GLP-1 receptor agonist alone. The muscle mass may comprise lean muscle mass.

**[0775]** In some embodiments, non-naturally occurring melanocortin analogs may improve a patient preference and/or compliance with relative to administration of a GLP-1 receptor agonist alone or otherwise without the non-naturally occurring melanocortin analog. The improved patient preference and/or compliance may comprise a preference for the administration route of the non-naturally occurring melanocortin analogs relative to the administration route of the GLP-1 receptor agonists. The administration route of the non-naturally occurring melanocortin analog may comprise a long-lasting injection, wherein the injection effects are maintained for a longer period of time relative to the effects from the GLP-1 receptor agonist.

**[0776]** The non-naturally occurring melanocortin analogs may serve as a GLP-1 receptor agonist (e.g., semaglutide or tirzepatide) alternative and/or a follow-on treatment to sustain or enhance weight loss, or otherwise prevent weight gain following administration of a GLP-1 receptor agonist. For example, the non-naturally occurring melanocortin analogs may serve as a substitute to GLP-1 receptor agonists by weight loss in subjects that were non-responsive to GLP-1 receptor agonists, reducing or preventing one or more side effects that are experienced from a GLP-1 receptor agonist, or reducing or preventing weight loss plateau that is experienced during or after administration of a GLP-1 receptor agonist. Such outcomes may be attributed to (1) lower doses of GLP-1 receptor agonists, (2) reduced frequency of administration of GLP-1 receptor agonists, (3) a reduced total duration of time of GLP-1 receptor agonist administration, or (4) a rescue effect of the non-naturally occurring melanocortin analogs, when the GLP-1 receptor agonists are administered in combination with the non-naturally occurring melanocortin analogs of the present technology, that is, when the non-naturally occurring melanocortin analogs are administered before, during, or

after administration of the GLP-1 receptor agonist. In some embodiments, after administration includes after completion of the GLP-1 receptor agonist treatment.

**[0777]** Additionally, the non-naturally occurring melanocortin analogs may promote one or more of a healthier weight loss (e.g., a weight loss with no or reduced unwanted side effects, less rapid weight loss) relative to weight loss experienced from administration of a GLP-1 receptor agonist and plateau-resistant dosing when administered as a monotherapy. In some embodiments, the non-naturally occurring melanocortin analog monotherapy comprises administration of a non-naturally occurring melanocortin analog to a subject that has not received a GLP-1 receptor agonist. In some embodiments, the monotherapy comprises administration of a non-naturally occurring receptor agonist to a subject that has, but is not currently receiving, a GLP-1 receptor agonist. In some embodiments, the non-naturally occurring melanocortin analog matches GLP-1 receptor agonist weight loss while maintaining food intake or while reducing a decrease in food intake that is observed with GLP-1 receptor agonist administration.

**[0778]** Administration of the non-naturally occurring melanocortin analogs of the present technology may comprise rebound-resistant weight loss (i.e., prevention of weight gain after treatment completion) and/or increased muscle retention when administered as a combination therapy with a GLP-1 receptor agonist, relative to a GLP-1 receptor agonist monotherapy. The rebound resistant weight loss may comprise a prevention or reduction in fat mass gain and/or BMI increase, relative to the GLP-1 receptor agonist monotherapy. In some embodiments, the combination therapy achieves the same weight loss as administration of the GLP-1 receptor agonist alone, but at a reduced dose or dosing frequency relative to the GLP-1 receptor agonist.

**[0779]** In some embodiments, the combination therapy comprises co-administration of the non-naturally occurring melanocortin analog and the GLP-1 receptor agonist. In some embodiments, the combination therapy comprises administering a non-naturally occurring melanocortin analog before or after a GLP-1 receptor agonist to a subject receiving a GLP-1 receptor agonist treatment.

**[0780]** The non-naturally occurring melanocortin agonist may be administered at any amount, frequency, duration, or combination with the GLP-1 receptor agonists as of the

present technology. Similarly, the GLP-1 receptor agonist may be administered at any amount, frequency, duration, or combination with the non-naturally occurring melanocortin agonist as of the present technology. In some embodiments, the non-naturally occurring melanocortin agonist is administered at a dose of about 10 to about 250 mg. The non-naturally occurring melanocortin agonist may be administered at a low dose to maintain weight (e.g., about 20 mg) or to prevent weight rebound (e.g., less than about 100 mg), relative to GLP-1 monotherapies. The non-naturally occurring melanocortin agonist may be administered at a high dose (e.g., about 200 mg) promote rapid weight loss. In some embodiments, the non-naturally occurring melanocortin analog is administered in combination with a GLP-1 receptor agonist to promote rapid weight loss without decreasing food intake as much as administration for the GLP-1 receptor agonist alone, wherein the dose of the GLP-1 agonist in combination with the non-naturally occurring melanocortin analog is reduced relative to the GLP-1 agonist administered as a monotherapy, to achieve the same or greater weight loss effect.

**[0781]**      *A07D and Semaglutide or Tirzepatide*

**[0782]**      In some embodiments, the non-naturally occurring melanocortin analog is A07D and the GLP-1 receptor agonist is semaglutide or tirzepatide.

**[0783]**      In some embodiments, administration of A07D comprises increased tolerance in a subject relative to administration of semaglutide monotherapy or tirzepatide monotherapy. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide. The increased tolerance may comprise reduced or prevented nausea relative to the semaglutide or tirzepatide monotherapies.

**[0784]**      In some embodiments, administration of A07D comprises increased muscle retention in a subject relative to administration of semaglutide monotherapy or tirzepatide monotherapy. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide. The increased muscle retention may comprise reduced or prevented muscle mass loss or increased muscle mass (e.g., lean muscle mass) relative to the semaglutide or tirzepatide monotherapies.

**[0785]** In some embodiments, administration of A07D comprises increased muscle retention in a subject relative to administration of semaglutide monotherapy or tirzepatide monotherapy. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide. The increased muscle retention may comprise reduced or prevented muscle mass loss or increased muscle mass (e.g., lean muscle mass) relative to the semaglutide or tirzepatide monotherapies.

**[0786]** In some embodiments, administration of A07D comprises increased preference and/or compliance with A07D administration in a subject relative to administration of semaglutide monotherapy or tirzepatide monotherapy. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide. The increased compliance/preference may comprise a long-lasting weight loss effect relative to the semaglutide or tirzepatide monotherapies.

**[0787]** In some embodiments, administration of A07D comprises reduced unwanted side effects, reduced weight loss plateau, and reduced weight loss rebound in a subject relative to administration of semaglutide monotherapy or tirzepatide monotherapy. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide. The increased muscle retention may comprise reduced or prevented muscle mass loss or increased muscle mass (e.g., lean muscle mass) relative to the semaglutide or tirzepatide monotherapies.

**[0788]** In some embodiments, administration of A07D comprises an improved weight loss (e.g., a healthier weight loss characterized by minimal muscle mass loss or maintained or increased muscle mass) in a subject relative to administration of semaglutide monotherapy or tirzepatide monotherapy. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide.

**[0789]** In some embodiments, administration of A07D comprises a rebound-resistant weight loss in a subject relative to administration of semaglutide monotherapy or tirzepatide monotherapy. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide. In some embodiments, the rebound-resistant weight loss comprises an increased or maintained muscle mass relative to the semaglutide monotherapy or tirzepatide monotherapy. In some

embodiments, the rebound-resistant weight loss comprises a reduction in muscle mass loss relative to the semaglutide monotherapy or tirzepatide monotherapy.

**[0790]** In some embodiments, administration of A07D comprises a reduced dose or reducing dosing frequency relative to the dose or dosing frequency of semaglutide monotherapy or tirzepatide monotherapy to achieve the same or improved weight loss effect. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide.

**[0791]** In some embodiments, administration of A07D comprises a reduced maintenance dose or maintenance dosing frequency the dose or dosing frequency of semaglutide monotherapy or tirzepatide monotherapy to achieve the same or improved weight maintenance and/or appetite suppression. In some embodiments, the administration of A07D comprises A07D monotherapy or A07D combination therapy with semaglutide or tirzepatide.

**[0792]** In some embodiments, the semaglutide monotherapy comprises a dose of about 0.10 mg to about 5.0 mg administered once weekly. In some embodiments the semaglutide monotherapy comprises a dose of 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, or 2.4 mg administered once weekly. In some embodiments, the semaglutide monotherapy comprises administering a 0.25 mg dose once weekly for 4 weeks, followed by a 0.5 mg dose administered once weekly for 4 weeks, followed by a 1.0 mg dose administered once weekly for 4 weeks, followed by a 1.7 mg dose administered once weekly for 4 weeks, followed by a 2.4 mg dose administered once weekly for 4 weeks. In some embodiments, the semaglutide monotherapy is administered subcutaneously.

**[0793]** In some embodiments, the tirzepatide monotherapy comprises a dose of about 0.5 mg to about 25 mg administered once weekly. In some embodiments the tirzepatide monotherapy comprises a dose of 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg administered once weekly. In some embodiments, the tirzepatide monotherapy comprises administering a 2.5 mg dose once weekly for 4 weeks, followed by a 5.0 mg dose administered once weekly for 4 weeks, followed by a 7.5 mg dose administered once weekly for 4 weeks, followed by a 10.0 mg dose administered once weekly for 4 weeks, followed by a 12.5 mg dose administered once weekly for 4 weeks, followed by a 15.0 mg dose



administered once weekly for 4 weeks. In some embodiments, the tirzepatide monotherapy is administered subcutaneously.

**[0794]** In some embodiments, the semaglutide monotherapy comprises a dose of about 0.25 to about 2 mg administered once daily. In some embodiments, the semaglutide monotherapy comprises administering a 0.25 mg dose administered once weekly for about 4 weeks, optionally increasing the dose to 0.5 mg administered weekly for at least 4 weeks, optionally increasing the dose to 1.0 mg administered once weekly for at least 4 weeks, optionally increasing the dose to 2 mg administered once weekly dose about 4 weeks. In some embodiments, the 3 mg dose is administered once daily. In some embodiments, the semaglutide monotherapy is administered subcutaneously.

**[0795]** In some embodiments, the semaglutide monotherapy comprises a dose of about 1.5 mg to about 25 mg administered once daily. In some embodiments, the semaglutide monotherapy comprises administering a 3.0 mg dose administered once daily for about 30 days, increasing the dose to 7.0 mg administered once daily for about 30 days, and optionally increasing the dose to 14 mg administered once daily for about 30 days. In some embodiments, the semaglutide monotherapy is administered orally.

**[0796]** *GLP-1 Receptor Agonist Monotherapies*

**[0797]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 0.10 mg to about 5.0 mg administered once weekly. In some embodiments the GLP-1 receptor agonist monotherapy comprises a dose of 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, or 2.4 mg administered once weekly. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 0.25 mg dose once weekly for 4 weeks, followed by a 0.5 mg dose administered once weekly for 4 weeks, followed by a 1.0 mg dose administered once weekly for 4 weeks, followed by a 1.7 mg dose administered once weekly for 4 weeks, followed by a 2.4 mg dose administered once weekly for 4 weeks. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is semaglutide.

**[0798]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 0.5 mg to about 25 mg administered once weekly. In some embodiments the GLP-1 receptor agonist monotherapy comprises a dose of 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg administered once weekly. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 2.5 mg dose once weekly for 4 weeks, followed by a 5.0 mg dose administered once weekly for 4 weeks, followed by a 7.5 mg dose administered once weekly for 4 weeks, followed by a 10.0 mg dose administered once weekly for 4 weeks, followed by a 12.5 mg dose administered once weekly for 4 weeks, followed by a 15.0 mg dose administered once weekly for 4 weeks. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is tirzepatide.

**[0799]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 0.5 mg to about 5 mg administered once weekly. In some embodiments the GLP-1 receptor agonist monotherapy comprises a dose of 0.75 mg, 1.5 mg, 3.0 mg, or 4.5 mg administered once weekly. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 0.75 mg dose once weekly for 4 weeks, followed by a 1.5 mg dose administered once weekly for 4 weeks, followed by a 3.0 mg dose administered once weekly for 4 weeks, followed by a 4.5 mg dose administered once weekly for 4 weeks. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is dulaglutide.

**[0800]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 2.5 µg to about 10 µg administered twice daily. In some embodiments the GLP-1 receptor agonist monotherapy comprises a dose of 5.0 µg or 10 µg administered twice daily. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 5.0 µg dose administered twice daily for about 30 days, followed by a 10 µg dose administered twice daily for about 30 days. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is exenatide.

**[0801]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 2.0 mg administered once weekly. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is exenatide.

**[0802]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 0.5 mg to about 5 mg. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 0.6 mg dose administered once daily for at least one week, optionally increasing the dose once weekly until a dose of 3 mg is reached. In some embodiments, the 3 mg dose is administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is liraglutide.

**[0803]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 0.25 to about 2 mg administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 0.25 mg dose administered once weekly for about 4 weeks, optionally increasing the dose to 0.5 mg administered weekly for at least 4 weeks, optionally increasing the dose to 1.0 mg administered once weekly for at least 4 weeks, optionally increasing the dose to 2 mg administered once weekly dose about 4 weeks. In some embodiments, the 3 mg dose is administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is semaglutide.

**[0804]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 5 µg to about 50 µg administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering about 20 µg or about 33 µg administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is lixisenatide.

**[0805]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 1.5 mg to about 25 mg administered once daily. In some embodiments, the

GLP-1 receptor agonist monotherapy comprises administering a 3.0 mg dose administered once daily for about 30 days, followed by optionally increasing the dose to 7.0 mg administered once daily for about 30 days. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 3.0 mg dose administered once daily for about 30 days, increasing the dose to 7.0 mg administered once daily for about 30 days, and optionally increasing the dose to 14 mg administered once daily for about 30 days. In some embodiments, the GLP-1 receptor agonist monotherapy is administered orally. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is semaglutide.

**[0806]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 5 µg to about 30 µg administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 10 µg dose administered once daily for about 14 days, and increasing the dose to 20 µg administered once daily for at least about 14 days. In some embodiments, the GLP-1 receptor agonist monotherapy is administered subcutaneously. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is lixisenatide.

**[0807]** In some embodiments, the GLP-1 receptor agonist monotherapy comprises a dose of about 3 mg to about 50 mg administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy comprises administering a 3 mg, 12 mg, 24 mg, 36 mg, or 45 mg dose administered once daily. In some embodiments, the GLP-1 receptor agonist monotherapy is administered orally. In some embodiments, the GLP-1 receptor agonist in the GLP-1 receptor agonist monotherapy is orforglipron.

**[0808]** *Maintenance Doses*

**[0809]** In some embodiments, a maintenance dose of the non-naturally occurring melanocortin agonist or the GLP-1 receptor agonist is administered to the subject to maintain weight and/or prevent weight rebound (i.e., weight gain following GLP-1 receptor agonist treatment). In some embodiments, the maintenance dose of the non-naturally occurring melanocortin analog comprises a reduced dose or dosing frequency relative to that of the GLP-1 receptor agonist maintenance dose to achieve the same or an improved result in weight maintenance or the prevention of weight rebound.

[0810] In some embodiments, the GLP-1 receptor agonist maintenance dose is 1.7 mg or 2.4 mg administered once weekly. In some embodiments, the GLP-1 receptor agonist is semaglutide.

*Subject Features*

[0811] In some embodiments, the subject has not received a weight loss agent.

[0812] In some embodiments, the subject has received a weight loss agent.

[0813] In some embodiments, the subject is receiving a weight loss agent.

[0814] In some embodiments, the subject has a body mass index (BMI) of greater than 24.9 kg/m<sup>2</sup>. In some embodiments, the subject has a BMI of 25 kg/m<sup>2</sup> to 29.9 kg/m<sup>2</sup>. In some embodiments, the subject has a BMI of greater than or equal to 30 kg/m<sup>2</sup>.

[0815] In some embodiments, the subject is an overweight subject. Overweight subjects include those having a body weight about 3% or more, 5% or more, 10% or more, 20% or more, or 30% or less, than the upper end of "normal" BMI (e.g., 24.9 kg/m<sup>2</sup>).

[0816] In some embodiments, the subject is an obese subject. Obese subjects include those having a BMI of greater than or equal to 30 kg/m<sup>2</sup>.

[0817] In some embodiments, the subject has a metabolic dysfunction. In other embodiments, the subject has another condition which is not metabolic dysfunction but administration of the weight loss agent provides therapeutic benefit to the non-metabolic dysfunction condition.

[0818] In some embodiments, the subject with a metabolic dysfunction has previously received treatment with the weight loss agent. A subject who has previously received treatment with the weight loss agent has completed at least one full treatment cycle with the weight loss agent. In other embodiments, the subject with a metabolic dysfunction is currently receiving treatment with the weight loss agent. A subject who is currently receiving treatment with the weight loss agent has received at least one dose of the weight loss agent. In still other embodiments, the subject with a metabolic dysfunction has not received any treatment with the weight loss agent. A subject who has not received any treatment with the weight loss agent has not received even a single dose of the weight loss agent.

**[0819]** In accordance with the present technology, a subject who has been treated with a weight loss agent has received a weight loss agent in an amount sufficient to induce at least minimum weight loss. Likewise, a subject how is currently undergoing treatment with a weight loss agent is receiving a weight loss agent in an amount sufficient to induce at least minimum weight loss.

**[0820]** In some embodiments, the subject has previously received treatment with the weight loss agent and has not lost body weight and/or fat mass. Alternatively, in some embodiments, the subject has previously received treatment with the weight loss agent and has lost body weight and/or fat mass. In such embodiments, the subject may still be overweight or obese. The subject may have stopped treatment with the weight loss agent because they were unable to continue losing body weight and/or fat mass with the weight loss agent.

**[0821]** In embodiments in which the subject has previously received treatment with the weight loss agent, the subject's body weight may be more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0822]** In embodiments in which the subject has previously received treatment with the weight loss agent, the subject's fat mass may be more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0823]** In some embodiments, the subject is currently receiving treatment with the weight loss agent and has not lost any body weight. Alternatively, in some embodiments, the subject is currently receiving treatment with the weight loss agent and has lost body weight and/or fat mass. In some embodiments, the subject is currently receiving treatment with the weight loss agent, has lost body weight and/or fat mass, and has failed to lose sufficient body weight and/or fat mass following administration of the weight loss agent. The subject who is currently receiving treatment with the weight loss agent may still be overweight or obese.

**[0824]** In embodiments in which the subject is currently receiving treatment with the weight loss agent, the subject's body weight may be more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0825]** In embodiments in which the subject is currently receiving treatment with the weight loss agent, the subject's fat mass may be more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0826]** In some embodiments, the subject has not received any treatment with the weight loss agent and has failed to lose sufficient or any weight using other weight loss methods. In some embodiments, the subject has not received any treatment with the weight loss agent and has not attempted to lose weight using any other methods. In such embodiments, the subject may begin treatment with the non-naturally occurring melanocortin agonist analog and the weight loss agent at the same time. A subject who begins administration of the weight loss agent and the non-naturally occurring melanocortin analog at the same time, and continues with concurrent administration of the two therapies, may experience greater body weight and/or fat mass loss compared to a subject who is administered only one of the therapies, e.g., only the weight loss agent or only the non-naturally occurring melanocortin analog.

**[0827]** In embodiments in which the subject begins treatment with the non-naturally occurring melanocortin analog and the weight loss agent at the same time, the subject's body weight may be more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, more than 40%, more than 45%, more than 50%, or more than 55% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0828]** In embodiments in which the subject begins treatment with the non-naturally occurring melanocortin analog and the weight loss agent at the same time, the subject's fat mass may be more than 10%, more than 15%, more than 20%, more than 25%, more than

30%, more than 35%, more than 40%, more than 45%, more than 50%, or more than 55% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[0829]** In some embodiments, the method prevents or reduces muscle mass loss (e.g., involuntary muscle mass loss) in the subject.

**[0830]** In some embodiments, the subject's muscle mass is not more than 5%, not more than 10%, not more than 15%, not more than 20%, not more than 25%, or not more than 30% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the weight loss agent.

**[0831]** In some embodiments, muscle mass of the subject is increased by at least 1% to 100% after the administration of the non-naturally occurring melanocortin analog or the pharmaceutical composition thereof. For example, muscle mass of the subject is increased by at least 1% to 100%, at least 5% to 75%, at least 10% to 50%, or at least 20% to 35%, after the treatment.

**[0832]** In some embodiments, muscle mass of the subject is increased by at least 5% to 15% after the administration. For example, muscle mass of the subject may be increased by at least 5% to 15%, at least 6% to 14%, at least 7% to 12%, or at least 8% to 9%, after the treatment.

**[0833]** In some embodiments, muscle mass of the subject is increased by at least 25% to 50% after the administration. For example, muscle mass of the subject may be increased by at least 25% to 50%, at least 28% to 48%, at least 25% to 45%, or at least 30% to 40%, after the treatment.

**[0834]** In some embodiments, the increased muscle mass is maintained for at least 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the treatment is stopped.

**[0835]** In some embodiments, the muscle mass is cardiac muscle mass, skeletal muscle mass, or both. In some embodiments, the cardiac muscle mass is determined by measuring change in heart weight. In some embodiments, the skeletal muscle mass is determined by measuring change in gastrocnemius tissue weight. In related embodiments,



the muscle mass change is cardiac muscle mass change, skeletal muscle mass change, or both. In some embodiments, cardiac muscle is determined by heart weight. In some embodiments, skeletal muscle mass is determined by gastrocnemius tissue weight. In some embodiments, the muscle mass changes may be assessed by using magnetic resonance imaging (MRI) and/or or nuclear magnetic resonance (NMR).

**[0836]** In some embodiments, the weight loss agent is administered to the subject for treating or preventing one of one or more metabolic dysfunctions. Nonlimiting examples of metabolic dysfunctions include obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome and metabolic myopathies.

**[0837]** In some embodiments of the methods of the present technology, the subject is a mammal, including but not limited to a human, a non-human primate such as a chimpanzee, a domestic livestock or a farm animal such as a cow, a bison, sheep, a pig, a goat, a horse, a chicken, and a rooster, a domestic pet animal such as a dog, a cat, a rat, a mouse, and a rabbit, and a laboratory subject such as a rodent, including a rat, a mouse, and a guinea pig. In some embodiments, the subject is a human. In some embodiments, the subject is an animal such as a rat or a dog.

## EXAMPLES

**[0838]** The following examples are intended to illustrate various embodiments of the present technology. As such, the specific embodiments discussed are not to be construed as limitations on the scope of the present technology. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of present technology, and it is understood that such equivalent embodiments, are to be included herein. Further, all references cited herein are hereby incorporated by reference in their entirety, as if fully set forth herein.

### **Example 1: Peptide Synthesis-Generic**

**[0839]** The non-naturally occurring melanocortin analogs of the present technology were synthesized by conventional procedures (e.g., solution-phase procedure, solid-phase synthesis) for the formation of a peptide linkage between amino acids. The solution-phase

procedure involved a condensation between the free alpha amino group of an amino acid or derivative thereof having the carboxyl group or other reactive groups protected and the free primary carboxyl group of another amino acid or derivative thereof having the amino group or other reactive groups protected. The solid-phase synthesis utilized a variety of resins and reagents and may involve additional purification steps.

**[0840]** The process for synthesizing the non-naturally occurring melanocortin analogs was generally performed by a procedure as follows. Each amino acid in the desired sequence of the non-naturally occurring melanocortin analogs was added one at a time in succession to another amino acid or derivative thereof or by a procedure whereby peptide fragments with the desired amino acid sequence were first synthesized conventionally and then condensed to provide the desired peptide. In most cases, the resulting peptide was then cyclized to yield a cyclic peptide.

**[0841]** Solid-phase peptide synthesis was carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain coupled to a solid-phase support according to the general principles of solid phase methods (see Merrifield, *Angew Chem.* 24:799-810 (1985) and Barany et al., *The Peptides, Analysis, Synthesis and Biology*, Vol. 2, Gross E. and Meienhofer J., Eds. Academic Press 1-284 (1980)). An exemplary solid-phase synthesis of non-naturally occurring melanocortin analogs is provided below.

**[0842]** Initially, the C-terminal amino acid residue of the non-naturally occurring melanocortin analog was coupled to a solid-phase support, e.g., a solid-phase resin. Coupling of the C-terminal amino acid residue and the solid-phase support may be carried out according to any method known in the art. Depending on the coupling method, the alpha-amine of the C-terminal amino acid residue may or may not be protected with an amine protecting group, as described below. Likewise, the carboxyl group of the amino acid residue may or may not be activated prior to coupling to the solid-phase support in order to increase its electrophilicity. Some methods of coupling rely on the formation of an ester bond between the carboxyl group of the amino acid and a reactive handle on the solid-phase resin. For example, an amino acid residue may be coupled to a p-benzyloxybenzyl alcohol resin (Wang) or a 2-chlorotriyl chloride resin via an ester linkage. Some methods of coupling rely

on the formation of an amide bond between the carboxyl group of the amino acid and a reactive handle on the solid-phase resin. For example, an amino acid residue may be coupled to a benzhydrylamine (BHA) resin through an Fmoc-linker such as, for example, p-[(R,S)- $\alpha$ -[1-(9H-fluorenyl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxyacetic acid (Rink linker) via an amide linkage.

**[0843]** The non-naturally occurring melanocortin analog was then synthesized by sequential amino acid addition or combination of peptide fragments. Subsequently, the peptide was cleaved from the solid-phase support and purified by methods known in the art, such as, for example, reverse phase high performance liquid chromatography (RP-HPLC) using a suitable column, such as a C18 column. Additionally, or alternatively, other methods of separation or purification were employed, including, but not limited to, methods based on the size or charge of the peptide. Once purified, the peptide was characterized by methods such as high-performance liquid chromatograph (HPLC), amino acid analysis, mass spectrometry, and the like.

#### **Example 2: Peptide Synthesis-Protecting Groups**

**[0844]** During synthesis of the non-naturally occurring melanocortin analogs, reactive side chain groups of the various amino acid residues were protected with suitable protecting groups, which prevented undesirable chemical reaction from occurring at that site until the protecting group was removed.

**[0845]** Additionally, protection of the alpha amino group of an amino acid residue or fragment was performed while that entity reacting with the carboxyl group, followed by the selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site. Specific protecting groups for solid phase synthesis methods and solution phase synthesis methods are known to those having ordinary skill in the art. Alpha amino groups were protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and

allyloxycarbonyl. Fmoc was also used for alpha amino protection. Guanidino groups, if present, were protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc was used as a protecting group for Arg.

**[0846]** Alpha aminoprotecting groups may be removed under basic conditions, such as, for example, using a solution of piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF). In synthesis methods in which alpha amino protecting groups were used, protecting groups were removed after synthesis of the peptide and before or after cleavage of the solid-phase support.

**Example 3: Peptide Synthesis-Additional Modifications**

**[0847]** If necessary, the peptides were further modified to obtain N-terminus modifications, such as acetylation, while on resin, or were removed from the resin by use of a cleaving reagent and then modified. Likewise, C-terminus modification (e.g., amidation), was performed if needed.

**[0848]** Additionally, the cyclized peptide structures were obtained prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains were deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP), were used for the cyclization. Suitable cyclic coupling reagents (e.g., 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1 (2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), N,N'-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt)) were also used for the cyclization. Coupling was initiated by a suitable base, such as N,N-diisopropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

**Example 4: Biological Data**

**[0849]** The agonist and antagonist activity of exemplary non-naturally occurring melanocortin analogs at the melanocortin receptors (e.g., MC1R, MC3R, MC4R, and MC5R) were measured via cAMP accumulation assay, according to the following procedure. Experimental design and execution were conducted by Epics Therapeutics S.A. EuroscreenFast (Bruxelles, Belgium).

*Compound Handling*

**[0850]** Compounds were delivered as powder (1 mg) or 10 mM solutions (100  $\mu$ l) in 100% DMSO. Powders were solubilized in 100% DMSO at a concentration of 10 mM (master solution) in a solvent volume defined. Serial dilutions were performed from master solution in 100% DMSO to obtain intermediate concentrations 200-, 300- or 400-fold higher than the concentrations to be tested, depending on the assay. Each sample was diluted 100-fold in the assay buffer and dispensed in a test plate. Amounts, solvents, and dilutions were estimated based on standard small-molecule drugs. Cell lines used for functional assays are shown in Table 1.

**Table 1.** Cell lines

| Receptor | Accession Number | Cell Line | Reference agonist  | Reference antagonist |
|----------|------------------|-----------|--------------------|----------------------|
| MC1R     | NP_002377.4      | CHO-K1    | NDP- $\alpha$ -MSH | N/A                  |
| MC3R     | AAC13541.1 I81V  | CHO-K1    | NDP- $\alpha$ -MSH | SHU9119              |
| MC4R     | NP_005903.2      | CHO-K1    | NDP- $\alpha$ -MSH | SHU9119              |
| MC5R     | NP_005904.1      | CHO-K1    | NDP- $\alpha$ -MSH | N/A                  |

*Compound Testing*

**[0851]** Compounds were tested for (i) agonist and/or antagonist activity at the human MC3 (FAST-0232C) and MC4 (FAST-0233C) receptors, (ii) agonist activity at the human MC1 (FAST-0230C) receptor, and/or (iii) agonist activity at the human MC5 (FAST-0233C) receptor at the following nanomolar concentrations, in duplicate: 0.0001, 0.001, 0.01, 0.03, 0.1, 0.3, 1, 10, 100, and 1,000.

*Testing Protocol*

**[0852]** Cyclic AMP (cAMP) Homogenous Time-Resolved Fluorescence (HTRF) assay for Gs coupled receptor:

**[0853]** CHO-K1 cells expressing recombinant human receptor grown prior to the test in media without antibiotic were detached by gentle flushing with PBS-EDTA (5 mM EDTA), recovered by centrifugation and resuspended in assay buffer (KRH: 5 mM KCl, 1.25 mM MgSO<sub>4</sub>, 124 mM NaCl, 25 mM HEPES, 13.3 mM Glucose, 1.25 mM KH<sub>2</sub>PO<sub>4</sub>, 1.45 mM CaCl<sub>2</sub>, 0.5 g/l BSA, supplemented with 1mM IBMX or 25μM Rolipram).

**[0854]** Dose response curves were performed in parallel with the reference compounds.

**[0855]** For agonist test (384well): 5 μl of cells were mixed with 5 μl of the test compound at increasing concentrations and then incubated 30 min at room temperature. After addition of the lysis buffer containing cAMP-d2 and anti-cAMP cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

**[0856]** For antagonist test (384well): 5 μl of cells were mixed in the wells of an assay plate with 5 μl of a mix of test compound at increasing concentrations and reference agonist for a final concentration corresponding to the historical EC<sub>80</sub>. The plates were then incubated 30 min at room temperature. After addition of the lysis buffer containing cAMP-d2 and anti-cAMP cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

#### *Quality Control for Compound Testing*

**[0857]** On each day of experimentation and prior to the testing of compounds, reference compounds were tested at several concentrations in duplicate (n=2) to obtain a dose-response curve and an estimated EC<sub>50</sub> and/or IC<sub>50</sub> values.

**[0858]** Reference values thus obtained for the test were compared to historical values obtained from the same receptor and used to validate the experimental session.

[0859] A session was considered as valid only if the reference value was found to be within a 0.5 logs interval from the historical value.

[0860] For replicate determinations, the maximum variability tolerated in the test was of +/-20% around the average of the replicates.

Non-naturally occurring melanocortin analog grouping

[0861] Non-naturally occurring melanocortin analogs were grouped based on structural similarities. Group E included non-naturally occurring melanocortin analogs E1 and E2, both of which are cyclic peptides comprising the motif c[Asp-Pro-Phe-Arg-Trp-Lys] (SEQ ID NO: 664) or a derivative thereof. Group E non-naturally occurring melanocortin analogs are provided in Table 2.

**Table 2.** Group E non-naturally occurring melanocortin analogs

| SEQ ID NO | Non-naturally occurring melanocortin analog | Formula                                                          |
|-----------|---------------------------------------------|------------------------------------------------------------------|
| 295       | E1                                          | Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>     |
| 297       | E2                                          | Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub> |

[0862] Group F included non-naturally occurring melanocortin analogs F1 to F20, all of which are cyclic peptides comprising the motif His-p(F)Phe-Arg-Trp. Further, group F peptides had an Emax value of greater than 85 on both the MC3R and MC4R. Group F non-naturally occurring melanocortin analogs are provided in Table 3.

**Table 3.** Group F non-naturally occurring melanocortin analogs

| SEQ ID NO | Non-naturally occurring melanocortin analog | Formula |
|-----------|---------------------------------------------|---------|
|           |                                             |         |

|     |     |                                                                           |
|-----|-----|---------------------------------------------------------------------------|
| 223 | F1  | Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>          |
| 460 | F2  | Ac-Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro-NH <sub>2</sub>         |
| 464 | F3  | Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>          |
| 465 | F4  | Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>          |
| 466 | F5  | Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>         |
| 467 | F6  | Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>          |
| 468 | F7  | Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>         |
| 469 | F8  | Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>      |
| 470 | F9  | Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH <sub>2</sub>          |
| 474 | F10 | Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH <sub>2</sub>     |
| 475 | F11 | Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH <sub>2</sub>     |
| 476 | F12 | Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub>          |
| 477 | F13 | Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub>      |
| 478 | F14 | Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH <sub>2</sub> |
| 481 | F15 | Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub>          |



|     |     |                                                                   |
|-----|-----|-------------------------------------------------------------------|
| 482 | F16 | Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub>  |
| 483 | F17 | Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub> |
| 484 | F18 | Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub>  |
| 485 | F19 | Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub> |
| 486 | F20 | Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub> |

**[0863]** Group G included non-naturally occurring melanocortin analogs G1 to G7, all of which are cyclic peptides comprising the motif His-p(F)Phe-Arg-Trp or a derivative thereof. Further, group G peptides had an E<sub>max</sub> value of greater than 85 on MC4R and an E<sub>max</sub> value less than 85 on MC3R. Group G non-naturally occurring melanocortin analogs are provided in Table 4.

**Table 4.** Group G non-naturally occurring melanocortin analogs

| SEQ ID NO | Non-naturally occurring melanocortin analog | Formula                                                               |
|-----------|---------------------------------------------|-----------------------------------------------------------------------|
| 471       | G1                                          | Ac-Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH <sub>2</sub> |
| 463       | G2                                          | Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>     |
| 462       | G3                                          | Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>      |
| 479       | G4                                          | Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub>      |
| 473       | G5                                          | Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH <sub>2</sub> |

|     |    |                                                                   |
|-----|----|-------------------------------------------------------------------|
| 480 | G6 | Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH <sub>2</sub> |
| 491 | G7 | Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>  |

**[0864]** Group H included non-naturally occurring melanocortin analog H1, which is a cyclic peptide comprising the motif His-p(Cl)Phe-Arg-Trp or a derivative thereof. The group H non-naturally occurring melanocortin analogs is provided in Table 5.

**Table 5.** Group H non-naturally occurring melanocortin analogs

| SEQ ID NO | Non-naturally occurring melanocortin analog | Formula                                                            |
|-----------|---------------------------------------------|--------------------------------------------------------------------|
| 498       | H1                                          | Ac-Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro-NH <sub>2</sub> |

**[0865]** Group I included non-naturally occurring melanocortin analogs I1 to I6, which are cyclic peptide comprising the motif His-dPhe-Arg-Trp-Lys, or a derivative thereof. Group I non-naturally occurring melanocortin analogs are provided in Table 6.

**Table 6.** Group I non-naturally occurring melanocortin analogs

| SEQ ID NO | Non-naturally occurring melanocortin analog | Formula                                                       |
|-----------|---------------------------------------------|---------------------------------------------------------------|
| 363       | I1                                          | Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>  |
| 365       | I2                                          | Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub> |
| 370       | I6                                          | Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>  |

|     |    |                                                                          |
|-----|----|--------------------------------------------------------------------------|
| 418 | I4 | Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH <sub>2</sub>         |
| 420 | I5 | Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub> |
| 621 | I3 | Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH <sub>2</sub>             |

[0866] Group J included non-naturally occurring melanocortin analogs J1 to J5, all of which are cyclic peptide comprising the motif Ala-His-dPhe-Arg, or a derivative thereof. Group J non-naturally occurring melanocortin analogs are provided in Table 7.

Table 7. Group J non-naturally occurring melanocortin analogs

| SEQ ID NO | Non-naturally occurring melanocortin analog | Formula                                                            |
|-----------|---------------------------------------------|--------------------------------------------------------------------|
| 268       | J1                                          | Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>  |
| 378       | J2                                          | Ac-Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>  |
| 379       | J3                                          | Ac-dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub> |
| 380       | J4                                          | Ac-Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH <sub>2</sub>   |
| 281       | J5                                          | Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-NH <sub>2</sub>            |

[0867] Group L included non-naturally occurring melanocortin analogs L1, which is a cyclic peptides comprising expanded N- and C- terminiNH<sub>2</sub>. The group L non-naturally occurring melanocortin analog is provided in Table 8.

Table 8. Group L non-naturally occurring melanocortin analogs

| SEQ ID NO | Non-naturally occurring | Formula |
|-----------|-------------------------|---------|
|-----------|-------------------------|---------|

|     |                            |                                                                       |
|-----|----------------------------|-----------------------------------------------------------------------|
|     | <b>melanocortin analog</b> |                                                                       |
| 639 | L1                         | Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH <sub>2</sub> |

Agonist activity of melanocortin analogs on melanocortin 3 receptor and melanocortin 4 receptor

**[0868]** Administration of all the non-naturally occurring melanocortin analogs activated melanocortin 3 receptor (MC3R) and melanocortin 4 receptor (MC4R) activity, as measured by cAMP levels (Table 9) .

**Table 9.** Dose-response results of melanocortin analogs and control against the melanocortin 3 receptor (MC3R) and melanocortin 4 receptor (MC4R) in agonist mode

| SEQ ID NO | Compound ID        | MC3R                  |           | MC4R                  |           |
|-----------|--------------------|-----------------------|-----------|-----------------------|-----------|
|           |                    | Max Activation (Emax) | EC50 (nM) | Max Activation (Emax) | EC50 (nM) |
|           | NDP- $\alpha$ -MSH | 106.05                | 0.17      | 103.19                | 0.07      |
| 223       | F1                 | 93.66                 | 0.11      | 101.94                | 0.05      |
| 268       | J1                 | 92.58                 | 30.14     | 101.65                | 2.89      |
| 363       | I1                 | 92.20                 | 0.73      | 101.05                | 0.67      |
| 365       | I2                 | 89.56                 | 81.32     | 111.15                | 7.84      |
| 370       | I6                 | 95.01                 | 0.58      | 104.98                | 0.03      |
| 378       | J2                 | 95.77                 | 9.24      | 99.72                 | 0.50      |
| 379       | J3                 | 88.91                 | 84.48     | 99.28                 | 6.50      |
| 380       | J4                 | 100.00                | 220.55    | 101.12                | 21.14     |
| 418       | I4                 | 97.17                 | 506.44    | 100.00                | 70.13     |
| 420       | I5                 | 100.16                | 169.79    | 100.41                | 28.96     |
| 460       | F2                 | 100.00                | 344.26    | 100.23                | 1.69      |
| 464       | F3                 | 93.45                 | 0.35      | 100.50                | 0.05      |
| 465       | F4                 | 96.34                 | 0.56      | 100.53                | 0.11      |

|     |     |        |        |        |         |
|-----|-----|--------|--------|--------|---------|
| 466 | F5  | 87.71  | 5.73   | 100.00 | 0.25    |
| 467 | F6  | 94.55  | 2.62   | 100.08 | 0.18    |
| 468 | F7  | 89.51  | 5.37   | 100.20 | 0.33    |
| 469 | F8  | 88.43  | 0.24   | 101.14 | 0.29    |
| 470 | F9  | 85.73  | 2.84   | 100.09 | 3.19    |
| 474 | F10 | 89.54  | 0.49   | 100.46 | 0.57    |
| 475 | F11 | 90.14  | 1.23   | 100.18 | 0.38    |
| 476 | F12 | 87.59  | 0.33   | 100.29 | 0.24    |
| 477 | F13 | 88.52  | 0.36   | 99.69  | 0.33    |
| 478 | F14 | 89.45  | 0.94   | 100.36 | 0.55    |
| 481 | F15 | 93.72  | 0.66   | 100.18 | 0.08    |
| 482 | F16 | 95.32  | 1.15   | 99.83  | 0.19    |
| 483 | F17 | 87.63  | 6.90   | 100.00 | 0.39    |
| 484 | F18 | 92.62  | 4.95   | 99.87  | 0.34    |
| 485 | F19 | 92.54  | 5.82   | 99.44  | 0.37    |
| 486 | F20 | 100.00 | 329.06 | 101.64 | 47.51   |
| 621 | I3  | 95.75  | 4.00   | 100.59 | 0.19    |
| 281 | J5  | 95.01  | 40.85  | 99.37  | 0.73    |
| 294 | E1  | 52.21  | 2.94   | 110.57 | 0.03    |
| 297 | E2  | 16.20  | -      | 57.48  | 3379.25 |
| 471 | G1  | 69.22  | 1.55   | 96.25  | 0.64    |
| 463 | G2  | 79.03  | 2.34   | 99.87  | 0.13    |
| 462 | G3  | 74.68  | 2.76   | 99.57  | 0.26    |
| 479 | G4  | 70.53  | 3.59   | 99.13  | 0.38    |
| 473 | G5  | 83.65  | 3.61   | 100.64 | 5.34    |
| 480 | G6  | 84.38  | 4.37   | 100.00 | 0.22    |
| 491 | G7  | 76.99  | 5.72   | 99.71  | 0.77    |
| 498 | H1  | 26.32  | 46.67  | 99.21  | 1.44    |
| 639 | L1  | 81.01  | 450.91 | 101.59 | 0.17    |

Agonist activity of melanocortin analogs on melanocortin 1 receptor and melanocortin 5 receptor

**[0869]** Administration of some non-naturally occurring melanocortin analogs activated melanocortin 1 receptor (MC1R) and melanocortin 5 receptor (MC5R) activity, as measured by cAMP levels. All the non-naturally occurring melanocortin analogs tested at MC1R had EC<sub>50</sub> values below 1 nM (Table 10).

**Table 10.** Dose-response results of melanocortin analogs and control against the melanocortin 1 receptor (MC1R) and the melanocortin 5 receptor

| SEQ<br>ID NO | Compound<br>ID     | MC1R                                     |                       | MC5R                                  |                       |
|--------------|--------------------|------------------------------------------|-----------------------|---------------------------------------|-----------------------|
|              |                    | Max<br>Activation<br>(E <sub>max</sub> ) | EC <sub>50</sub> (nM) | Max Activation<br>(E <sub>max</sub> ) | EC <sub>50</sub> (nM) |
|              | NDP- $\alpha$ -MSH | 101.06                                   | 0.39                  | 101.44                                | 0.12                  |
| 223          | F1                 | 100.02                                   | 0.01                  | 101.26                                | 0.06                  |
| 268          | J1                 | 102.19                                   | 0.06                  | 100.00                                | 659.75                |
| 363          | I1                 | 101.95                                   | 0.02                  | 100.19                                | 0.45                  |
| 365          | I2                 | 103.24                                   | 4.48                  | 100.71                                | 23.35                 |
| 370          | I6                 | 102.70                                   | 0.01                  | 104.56                                | 0.02                  |
| 378          | J2                 | 101.61                                   | 0.01                  | 102.64                                | 15.80                 |
| 379          | J3                 | 103.00                                   | 0.12                  | 100.00                                | 625.61                |
| 380          | J4                 | 101.52                                   | 0.24                  | 100.00                                | 572.13                |
| 418          | I4                 | 101.98                                   | 0.03                  | 98.73                                 | 154.52                |
| 420          | I5                 | 102.19                                   | 0.59                  | 100.00                                | 504.39                |
| 460          | F2                 | 101.37                                   | 0.14                  | 103.21                                | 1.82                  |
| 464          | F3                 | 100.40                                   | 0.01                  | 103.20                                | 0.81                  |
| 465          | F4                 | 100.35                                   | 0.01                  | 101.71                                | 0.95                  |
| 466          | F5                 | 101.08                                   | 0.02                  | 101.05                                | 3.70                  |

|     |     |        |      |        |         |
|-----|-----|--------|------|--------|---------|
| 467 | F6  | 100.11 | 0.03 | 102.66 | 3.04    |
| 468 | F7  | 101.92 | 0.04 | 102.60 | 8.83    |
| 469 | F8  | 101.68 | 0.01 | 103.49 | 0.01    |
| 470 | F9  | 102.90 | 0.07 | 102.60 | 0.44    |
| 474 | F10 | 104.17 | 0.01 | 101.71 | 0.20    |
| 475 | F11 | 102.78 | 0.01 | 101.46 | 0.41    |
| 476 | F12 | 99.42  | 0.00 | 102.04 | 0.02    |
| 477 | F13 | 104.93 | 0.01 | 102.90 | 0.02    |
| 478 | F14 | 104.27 | 0.01 | 101.87 | 0.40    |
| 481 | F15 | 104.99 | 0.01 | 101.02 | 0.64    |
| 482 | F16 | 104.19 | 0.00 | 103.47 | 1.19    |
| 483 | F17 | 106.13 | 0.02 | 102.13 | 4.10    |
| 484 | F18 | 104.45 | 0.01 | 101.83 | 1.80    |
| 485 | F19 | 105.28 | 0.01 | 100.50 | 4.16    |
| 486 | F20 | 102.45 | 0.89 | 97.19  | 6.01    |
| 621 | I3  | 101.15 | 0.01 | 99.10  | 0.91    |
| 281 | J5  | 101.67 | 0.15 | 100.00 | 2607.20 |
| 471 | G1  | 101.22 | 0.01 | 99.79  | 0.10    |
| 463 | G2  | 100.72 | 0.01 | 101.64 | 1.67    |
| 462 | G3  | 101.59 | 0.02 | 101.07 | 0.83    |
| 479 | G4  | 104.22 | 0.01 | 102.27 | 1.01    |
| 473 | G5  | 103.79 | 0.11 | 102.62 | 1.01    |
| 480 | G6  | 104.33 | 0.00 | 104.22 | 1.28    |
| 491 | G7  | 103.05 | 0.03 | 103.74 | 0.05    |
| 498 | H1  | 103.43 | 0.14 | 103.18 | 0.15    |
| 639 | L1  | 103.99 | 0.37 | 103.67 | 0.29    |

**Example 5: Cardiac Activation of Melanocortin Agonists**

**[0870]** The effect of the melanocortin agonists on cardiac activation in rats was tested using E2 (SEQ ID NO:295) according to the following procedure. Baseline measurements of heart rate, systolic blood pressure, and diastolic blood pressure of rats were taken 15 minutes prior to administration of E2. The rats were then administered saline, 3 mg/kg E2, or 6 mg/kg E2 via subcutaneous injection and the heart rate, systolic blood pressure, and diastolic blood pressure were measured at the following time points post injection: 5 minutes, 15 minutes, 30 minutes, 60 minutes, 120 minutes, and 180 minutes.

**[0871]** FIGS. 1A-1C show the cardiac activation data from 15 minutes before subcutaneous injection of E2 to 180 minutes after injection of E2. As shown in FIG. 1A, the heart rate of rats administered 3 mg/kg E2 (G1) decreased directly after injection, increased steadily from 30 minutes to 120 minutes, and then decreased again at 180 minutes to just slightly above the starting heart rate (i.e., at -15 min). Rats administered 6 mg/kg E2 (G2) maintained a steady heart rate until 120 minutes after injection when an increase in heart rate may be seen, however, the final heart rate of G2 rats was similar to that of G1 and control (G3) rats.

**[0872]** As may be seen in FIG. 1B the systolic blood pressure (SBP) of the rats in each group was similar for all time points, with a slight increase overall after injection for all three groups. The diastolic blood pressure (DBP) of rats administered 3 mg/kg E2 and 6 mg/kg E2 was higher than the diastolic blood pressure of the control rats at all time points post injection, however, no group of rats had a diastolic blood pressure above 100 at any time point (FIG. 1C).

**[0873]** This data suggests that melanocortin agonists in accordance with the present technology such as E2 avoid cardiac activation, which has been seen in earlier peptide and small molecule agonists of the melanocortin receptors.

**Example 6: Effect of Melanocortin Agonist on Appetite Suppression**

**[0874]** The effect of melanocortin agonists on appetite suppression in rats was tested using E2 (SEQ ID NO: 295) and compared to setmelanotide (Imcivree®). In this study, rats were administered saline (control group); 3 mg/kg E2; 10 mg/kg E2; or 1 mg/kg setmelanotide. Administration was performed via subcutaneous injection.



[0875] FIGS. 2A-2C show the body weight and food intake of the rats in each treatment group. The body weight of rats was recorded 14 days before injection, 3 days before injection, 2 days before injection, 1 day before injection, the day of injection, and 1 day after injection. The body weight of the rats in each group followed the same trajectory until 1 day after injection, when the body weight of rats administered 3 mg/kg 2, 10 mg/kg E2, and 1 mg/kg setmelanotide was lower than the body weight of rats in the control group.

[0876] As shown in FIG. 2B, the net gain food intake was highest at each time point post injection for rats administered saline and, at 24 hours post injection, rats administered 1 mg/kg setmelanotide had increased net gain food intake relative to rats administered 3 mg/kg or 10 mg/kg E2. FIG. 2C shows that rats that were administered 3mg/kg E2, 10 mg/kg E2, or 1 mg/kg setmelanotide had significantly lower cumulative food intake than rats administered saline up to 24 hours post injection.

**Example 7: Effect of Melanocortin Antagonists on Plasma Insulin**

[0877] The effect of melanocortin antagonists on plasma insulin levels in rats was tested using B07 (SEQ ID NO: 3). Baseline plasma insulin levels of rats were recorded before administration of B07. Then, B07 was administered to rats via subcutaneous injection. Following injection of B07, the plasma insulin levels of the rats were measured again to determine the effect of the melanocortin antagonist.

[0878] FIGS. 3A and 3B depict the insulin plasma insulin levels of rats pre and post subcutaneous injection of B07. As may be seen, there was minimal change in insulin levels following administration of the melanocortin antagonist.

**Example 8: Combination Therapy Rat Study in a High Fat Diet Model**

[0879] The efficacy of combination therapies in accordance with the present technology will be tested in a rat model of obesity using a high fat diet Sprague Dawley rat model.

[0880] Test articles, positive controls, and vehicle information is outlined in Table 21 and Table 22.

Table 21: Test Articles and Positive Control Information

|                           |         |             |             |
|---------------------------|---------|-------------|-------------|
| <b>Name</b>               | A07D    | Semaglutide | Tirzepatide |
| <b>MW</b>                 | 1180.42 | 4113.64     | 4813.53     |
| <b>FW</b>                 | 1239.68 | 4113.64     | 4813.53     |
| <b>Purity</b>             | 95%     | 99.84%      | 98.65%      |
| <b>Storage Conditions</b> | -20°C   | -80°C       | -80°C       |

Table 22: Vehicle Information

|                            |        |
|----------------------------|--------|
| <b>Name:</b>               | Saline |
| <b>Physical State:</b>     | Liquid |
| <b>Storage Conditions:</b> | RT     |

*Test article preparation*

**[0881] Semaglutide-25 nmol/kg (0.052 mg/mL, 2 ml/kg):** 3.616 mg of Semaglutide powder was weighed and dissolved in 70.20 mL of saline. The Semaglutide solution was vortexed and stirred for 10 min to obtain a uniform clarified solution. The Semaglutide-25 nmol/kg was prepared once and divided into 3 bottles, respectively, and stored at -80°C for later use.

**[0882] Semaglutide-12.5 nmol/kg (0.026 mg/mL, 2 ml/kg):** 1.205 mg of Semaglutide powder was weighed and dissolved in 46.80 mL of saline, The Semaglutide solution was vortexed and stirred for 10 min to obtain a uniform clarified solution. The Semaglutide-12.5 nmol/kg was prepared once and divided into 3 bottles, respectively, and stored at -80°C for later use.

**[0883] Tirzepatide-25 nmol/kg (0.061 mg/mL, 2 ml/kg):** 4.282 mg of Tirzepatide powder was weighed and dissolved in 70.20 mL of saline. The Tirzepatide solution was vortexed and stirred for 10 min to obtain a uniform clarified solution. The Tirzepatide-25

nmol/kg was prepared once and divided into 3 bottles, respectively, and stored at -80°C for later use.

**[0884] Tirzepatide-12.5 nmol/kg (0.030 mg/mL, 2 ml/kg):** 1.427 mg of Tirzepatide powder was weighed and dissolved in 46.80 mL of saline. The Tirzepatide solution was vortexed and stirred for 10 min to obtain a uniform clarified solution. The Tirzepatide-12.5 nmol/kg was prepared once and divided into 3 bottles, respectively, and stored at -80°C for later use.

**[0885] A07D-3mpk (1.658 mg/mL, 2 ml/kg):** 205.65 mg of A07D powder was weighed and dissolved in 124.02 mL of saline. The A07D solution was vortexed and stirred for 10 min to obtain a uniform clarified solution, then 1 N NaOH or 1 N HCl was added to adjust the pH to 5.0-6.0. The formulation was prepared twice a week and stored at 2-8 °C.

**[0886] A07D-1mpk (0.553 mg/mL, 2 ml/kg):** 12 mL of A07D-3mpk was dissolved in 24 mL of saline. The formulation was prepared twice a week and stored at 2-8 °C.

#### *Study Information*

**[0887]** Animal information and diets are outlined in Table 23 and Table 24.

Table 23: Animal Information

|                                 |                                                                  |
|---------------------------------|------------------------------------------------------------------|
| <b>Species</b>                  | SD rats                                                          |
| <b>Level</b>                    | SPF                                                              |
| <b>Weight (ordered)</b>         | 100g-130g                                                        |
| <b>Weight (Study began)</b>     | ~180g                                                            |
| <b>Sex</b>                      | Male                                                             |
| <b>Method of Identification</b> | The rat will be singly housed per cage with a unique cage number |
| <b>Animal Number (ordered)</b>  | 84                                                               |
| <b>Animal Number (used)</b>     | 72                                                               |

Table 24: Animal Diets

| Diets              | High fat diets (D12451)                               | Kaolin (XT19031)                 |
|--------------------|-------------------------------------------------------|----------------------------------|
| Formulas           | 45% kcal fat, 35% kcal carbohydrate, 20% kcal protein | Kaolin, USP, 99% + Acacia Gum 1% |
| Storage Conditions | -20°C                                                 | -20°C                            |

*Study Design*

**[0888]** 84 SD rats were used. After arriving at the facility, rats were raised with the temperature maintained at 20-24 °C and humidity maintained at 40-70%. Temperature and relative humidity were monitored daily. An electronic time-controlled lighting system was used to provide a 12-hour light/12-hour dark cycle, 19:00 pm – 7:00 am, lights out. Rats were housed individually in a plastic cage. Enrichment toys were provided. Rats were fed a normal diet and fresh water during acclimation; animals were acclimated in the testing facility for one week before the modeling.

**[0889]** After 1 week acclimation, 84 SD rats were fed high fat diet (HFD) (45% kcal fat, 35% kcal carbohydrate, and 20% kcal protein) for 3 weeks. During the whole feeding process, the animals were free to eat and drink. Body weight was measured weekly, and food was added three times a week.

**[0890]** Group Design: 72 SD rats were selected and assigned to 7 dose groups (Day0) according to body weight, food intake kaolin intake and body composition.

**[0891]** Dose Groups:

1. A07D-1mpk
2. A07D-3mpk
3. Saline control
4. Semaglutide
5. A07D-3mpk + Semaglutide
6. A07D-3mpk + Tirzepatide

## 7. Tirzepatide

*Dose Protocol*

[0892] Dose protocols are outlined in Table 25.

Table 25: Dose Protocols

| Group | Treatment                                                       | Dose Level (mg/kg) | Route        | Frequency                       | Animal number              |
|-------|-----------------------------------------------------------------|--------------------|--------------|---------------------------------|----------------------------|
| 1     | A07D-1mpk                                                       | 1                  | s.c.         | QD*5 Weeks                      | 10 (halved to 5 at week 4) |
| 2     | A07D-3mpk                                                       | 3                  | s.c.         | QD*5 Weeks                      | 12 (halved to 6 at week 4) |
| 3     | Saline control                                                  | -                  | s.c.         | QD*5 Weeks                      | 10                         |
| 4     | Semaglutide-12.5/25 nmol/kg                                     | 0.051/0.103        | s.c.         | Q3D*5 Weeks                     | 10 (halved to 5 at week 4) |
| 5     | A07D-3mpk+ Semaglutide-12.5/25 nmol/kg                          | 3<br>0.051/0.103   | s.c.<br>s.c. | QD*5 Weeks<br>Q3D*5 Weeks       | 10 (halved to 5 at week 4) |
| 6     | A07D-3mpk+ Tirzepatide-12.5/25 nmol/kg                          | 3<br>0.060/0.120   | s.c.<br>s.c. | QD*5 Weeks<br>Q3D*5 Weeks       | 10 (halved to 5 at week 4) |
| 7     | Tirzepatide-12.5/25 nmol/kg                                     | 0.060/0.120        | s.c.         | Q3D*5 Weeks                     | 10 (halved to 5 at week 4) |
| 1'    | Saline (group starts at Week 4 with half the rats from Group 1) | -                  | s.c.         | QD*2 Weeks (starting at week 4) | 5                          |
| 2'    | Saline (group starts at Week 4 with half the rats from Group 2) | -                  | s.c.         | QD*2 Weeks (starting at week 4) | 6                          |
| 4'    | Saline (group starts at Week 4 with half the rats from Group 4) | -                  | s.c.         | QD*2 Weeks (starting at week 4) | 5                          |

|    |                                                                    |   |      |                                 |   |
|----|--------------------------------------------------------------------|---|------|---------------------------------|---|
| 5' | A07D 3mpk (group starts at Week 4 with half the rats from Group 5) | 3 | s.c. | QD*2 Weeks (starting at week 4) | 5 |
| 6' | A07D 3mpk (group starts at Week 4 with half the rats from Group 6) | 3 | s.c. | QD*2 Weeks (starting at week 4) | 5 |
| 7' | Saline (group starts at Week 4 with half the rats from Group 7)    | - | s.c. | QD*2 Weeks (starting at week 4) | 5 |

s.c. = subcutaneous

### *Study Procedure*

#### (1) Acclimation and Grouping

**[0893]** Day-4~day-1: 84 SD rats were mock dosed for 3 days, and body weight, food intake, kaolin intake, and body composition were measured to establish a baseline.

**[0894]** Day-1: 72 animals were selected and assigned into 7 groups based on the animals' baseline body weight, food intake, kaolin intake and body composition.

#### (2) Body weight, Food intake, Kaolin intake

**[0895]** Day1-day14: The body weight, food intake and kaolin intake of rats were measured daily in the afternoon.

#### (3) Dosing

**[0896]** The rats dosed with test article refer to dose protocol.

**[0897]** Dosing Groups:

**[0898]** Group 1: Subcutaneous injection with A07D-1mpk was dosed QD (Day0-34).

**[0899]** Group 2: Subcutaneous injection with A07D-3mpk was dosed QD (Day0-34).

**[0900]** Group 3: Subcutaneous injection with saline was dosed QD (Day0-34).

**[0901]** Group 4: Subcutaneous injection with Semaglutide-12.5 nmol/kg was dosed Q3D (Day 0, Day 3) and subcutaneous injection with Semaglutide-25 nmol/kg was dosed Q3D (Day 6, Day 9, Day 12, Day 15, Day 18, Day 21, Day 24, Day 27, Day 30, Day 33).

**[0902]** Group 5: Subcutaneous injection with A07D-3mpk was dosed QD (Day0-34), Subcutaneous injection with Semaglutide-12.5 nmol/kg was dosed Q3D (Day 0, Day 3) and subcutaneous injection with Semaglutide-25 nmol/kg was dosed Q3D (Day 6, Day 9, Day 12, Day 15, Day 18, Day 21, Day 24, Day 27, Day 30, Day 33).

**[0903]** Group 6: Subcutaneous injection with A07D-3mpk was dosed QD (Day0-34), Subcutaneous injection with Tirzepatide-12.5 nmol/kg was dosed Q3D (Day 0, Day3) and subcutaneous injection with Tirzepatide-25 nmol/kg was dosed Q3D (Day 6, Day 9, Day 12, Day 15, Day 18, Day 21, Day 24, Day 27, Day 30, Day 33).

**[0904]** Group 7: Subcutaneous injection with Tirzepatide-12.5 nmol/kg was dosed Q3D (Day 0, Day 3) and subcutaneous injection with Tirzepatide-25 nmol/kg was dosed Q3D (Day 6, Day 9, Day 12, Day 15, Day 18, Day 21, Day 24, Day 27, Day 30, Day 33).

(4) Body composition

**[0905]** On Day-1, Day7, Day13, Day 19, Day28, Day 34: Fat, fluid and lean mass was recorded by Bruker's minispec.

(5) Oral glucose tolerance test

**[0906]** On Day 0, Day 8, Day 19: Rats were placed in new cages and fasted for 5-6 hours, then glucose was oral gavaged with 3 g/kg at a dose volume of 6 ml/kg. Blood glucose levels were measured at 0 (pre-dose), 15-, 30-, 60- and 120-min post of glucose dosing. Time-Blood Glucose curve AUCs were calculated. Following the OGTT, rats were be returned to their normal cages and provided free access to food and water.

(6) Clinical observation

**[0907]** Clinical observations are outlined in Table 26.

Table 26: Day 1-Day 34 Clinical observations

|                    |                                                                                                                                                          |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| General Appearance | Dehydration, decreased body weight, missing anatomy, abnormal posture, hypothermia, fractured appendage, swelling, tissue masses, prolapse, paraphimosis |
| Skin and Fur       | Discoloration, urine stain, pallor, redness, cyanosis, icterus, wound, sore, abscess, ulcer, alopecia, ruffled fur                                       |
| Eyes               | Exophthalmos, microphthalmia, ptosis, reddened eye, lacrimation, discharge, opacity                                                                      |

|                      |                                                        |
|----------------------|--------------------------------------------------------|
| Nose, mouth and head | Head tilted, nasal discharge, malocclusion, salivation |
| Respiration          | Sneezing, dyspnea, tachypnea, rales                    |
| Urine                | Discoloration, blood in urine, polyuria, anuria        |
| Feces                | Discoloration, blood in the feces, softness/diarrhea   |
| Locomotor            | Hyperactivity, coma, ataxia, circling, muscle, tremors |

## (7) Terminal

**[0908]** Day 35: After measuring body weight and food remains, animals were euthanized with CO<sub>2</sub>, whole blood was collected via heart puncture, and 300µl of whole blood was transferred into the EDTA-2K pre-chilled microcentrifuge tubes. The blood with EDTA-2K was centrifuged at 7000 rpm for 10 min (at 4 °C) to collect 100 µl plasma. The rest of the whole blood was transferred into tubes without anticoagulants for 30 min and was centrifuged at 3000 xg for 10 min to collect 150 µ serum. Both plasma and serum samples were stored at -80 °C.

**[0909]** Tissue collection: At the end of study, gastrocnemius muscle, perirenal fat, epididymal fat and brain were collected and weighed, and stored at -80 °C.

**[0910]** For two weeks prior to the study and for the duration of the study, rats were fed a high fat diet (45% fat). During the study, rats received saline, A07D, GLP-1, or A07D + GLP-1. to assess the weight loss efficacy of A07D, as well as A07D + GLP-1 combination therapy, for 5 weeks. The GLP-1's used included Tirzepatide and Semaglutide.

**[0911]** Regrouping: Day 0 indicated the start of treatment. On Day 7, the dose of GLP-1 increased from 12.5 nmol/kg to 25 nmol/kg. On Day 21, rats were regrouped, where Group 2 had 6 rats removed from A07D treatment, and Groups 3 and 4 had 5 rats removed from GLP-1 treatment. Day 35 indicated the end of study.

**[0912]** Regrouping procedures are further detailed in Table 27.

Table 27: Study Dosing

| Group | Treatment      | Dose Level (mg/kg) | Frequency  | Number of Rats |
|-------|----------------|--------------------|------------|----------------|
| 1     | Saline control | -                  | QD*5 Weeks | 10             |



|   |                                          |                    |                           |                                                            |
|---|------------------------------------------|--------------------|---------------------------|------------------------------------------------------------|
| 2 | A07D-3mpk                                | 3                  | QD*5 Weeks                | 12 (half taken off A07D at Day 21 to be given saline)      |
| 3 | GLP-1-12.5/25 nmol/kg                    | 0.051/0.103        | Q3D*5 Weeks               | 10 (half taken off GLP-1 at Day 21 to be given saline)     |
| 4 | A07D-3mpk +<br>GLP-1-<br>12.5/25 nmol/kg | 3 +<br>0.051/0.103 | QD*5 Weeks<br>Q3D*5 Weeks | 10 (half taken off GLP-1 at Day 21 to be given A07D, only) |

#### *Data Processing and Analysis*

**[0913]** All values were expressed as mean  $\pm$  S.E.M. Statistical analyses were performed by one-way ANOVA or two-way ANOVA. A p value of less than 0.05 was considered statistically significant.

#### *Protocol Amendments and Deviations*

**[0914]** Changes to the approved protocol will be in the form of amendments approved by the Study Director and the Sponsor. Amendments will clearly describe the protocol changes and will include the effective date of the change and the justification for the change. All unintentional deviations from the protocol and the reasons for the deviations will be documented and acknowledged by the Study Director. The Sponsor's Representative will be promptly informed of the occurrence of any deviations that might affect the results of the study, and any corrective actions taken.

#### *Results*

**[0915]** FIGS. 4A-4N show the change in body weight for rats in Groups 2, 3, 4, and 5. Rats administered 3 mpk E2 and semaglutide (Group 5) demonstrated a greater reduction in body weight after 11 days of treatment compared to rats administered 12.5/25 nmol/kg semaglutide ("Sema"; Group 4) or 3mpk E2 (Group 2) alone.

**[0916]** The mass distribution of rats in Groups 2, 3, 4, and 5 after 7 and 13 days of treatment is shown in FIGS. 5A-5I. FIGS. 5A, 5C, 5D, 5E, 5G show the fat mass, average daily change in fat mass, lean mass, average daily change in lean mass, and fluid mass of the rats in grams. FIGS. 5B and 5H show the fat mass and fluid mass as percent body

weight, normalized to the individual animal weight on the day of the measurement. As shown in FIGS. 5A and 5B, rats that received both E2 and semaglutide experienced a greater reduction in fat mass (grams and percent body weight) as compared to rats that received E2 or semaglutide alone. Notably, rats treated with E2 and semaglutide also maintained a higher percentage of lean mass compared to rats in Groups 2, 3, and 4 (FIG. 5D). The fluid mass of rats was similar across all treatment groups at 7 days but was reduced for rats administered semaglutide or a combination of semaglutide and E2 at 13 days (FIGS. 5G and 5H). FIG. 5I shows the week 5 average daily change in fat mass of the rats in grams.

**[0917]** FIGS. 6A-6E show the cumulative food intake, daily food intake, and kaolin intake of rats in Groups 2, 3, 4, and 5. As shown in FIGS. 6A-6E, rats receiving a combination of E2 and semaglutide had the lowest cumulative food consumption of all rats after 11 days and had comparative kaolin intake to rats that received semaglutide alone. These results indicate that the combination of E2 and semaglutide is similarly effective, if not more effective, at suppressing appetite as semaglutide.

**[0918]** The blood glucose levels of rats in Groups 2, 3, 4, and 5 following an oral glucose tolerance test on day 0 and day 8 are shown in FIGS. 7A-7D. On day 0, blood glucose levels were substantially similar among rats in all treatment groups (FIG. 7A). In contrast, on day 8, rats in Groups 2, 4, and 5 had significantly lower blood glucose levels following the oral glucose tolerance test than control rats (FIGS. 7B and 7C). Further, rats receiving a combination of E2 and semaglutide had similar blood glucose levels as rats receiving semaglutide alone (FIGS. 7B-7D).

**[0919]** FIGS. 8A-8N show the change in body weight for rats in Groups 2, 3, 6, and 7. Rats administered 3 mpk E2 and 12.5/25 nmol/kg tirzepatide (Group 6) demonstrated a greater reduction in body weight after 11 days of treatment compared to rats administered 12.5/25 nmol/kg tirzepatide ("Tirzep"; Group 7) or E2 (Group 2) alone.

**[0920]** The mass distribution of rats in Groups 2, 3, 6, and 7 after 7 and 13 days of treatment is shown in FIGS. 9A-9I. FIGS. 9A, 9C, 9D, 9F, and 9G show the fat mass, average daily change in fat mass, lean mass, average daily change in lean mass, and fluid mass of the rats in grams and FIGS. 9B, 9E, and 9H show the fat mass, lean mass, and fluid

mass of the rats as percent body weight, normalized to the individual animal weight on the day of the measurement. As shown in FIGS. 9A and 9B, rats that received both E2 and tirzepatide experienced a greater reduction in fat mass (grams and percent body weight) as compared to rats that received E2 or ortirzepatide alone. Notably, rats treated with E2 and tirzepatide also maintained a higher percentage of lean mass compared to rats in Groups 2, 3, and 7 (FIG. 9E). The fluid mass of rats was similar across all treatment groups at 7 days but was reduced for rats administered a combination of tirzepatide and E2 at 13 days (FIGS. 9G and 9H). FIG. 9I shows the week 5 average daily change in fat mass of the rats in grams.

**[0921]** FIGS. 10A-10E show the cumulative food intake, daily food intake, and kaolin intake of rats in Groups 2, 3, 6, and 7. As shown in FIGS. 10A-10E, rats receiving a combination of E2 and tirzepatide had the lowest cumulative food consumption after 11 days and had comparative kaolin intake to rats that received tirzepatide alone. These results indicate that the combination of E2 and tizepatide is similarly effective, if not more effective, at suppressing appetite as tirzepatide.

**[0922]** The blood glucose levels of rats in Groups 2, 3, 6, and 7 following an oral glucose tolerance test on day 0 and day 8 are shown in FIGS. 11A-11D. On day 0, blood glucose levels were substantially similar among rats in all treatment groups (FIG. 11A). In contrast, on day 8, rats in Groups 2, 6, and 7 had significantly lower blood glucose levels following the oral glucose tolerance test than control rats (FIGS. 11B and 11C). Further, rats receiving a combination of E2 and tirzepatide had similar blood glucose levels as rats receiving tirzepatide alone (FIGS. 11B-11D).

**[0923]** FIGS. 12A-12F show the change in body weight for rats in Groups 1, 2, and 3. As shown in FIGS. 12A-12F, rats administered 3 mpk E2 (Group 2) exhibited a lower body weight after 11 days of treatment compared to rats administered 1 mpk E2 (Group 1). Both Group 1 and Group 2 had significantly lower body weight after 8 days of treatment than control rats (Group 3).

**[0924]** The mass distribution of rats in Groups 1, 2, and 3 after 7 and 13 days of treatment is shown in FIGS. 13A-13F, including the fat mass, lean mass, and fluid mass of the rats in grams and the fat mass, lean mass, and fluid mass of the rats as percent body weight, normalized to the individual animal weight on the day of the measurement. As

shown in FIGS. 13A and 13B, rats that received 1 mpk E2 had similar fat mass as rats that received 3 mpk E2. Rats in both treatment groups (Groups 1 and 2) exhibited lower fat mass than control rats. Rats in Groups 1 and 2 had slightly higher percent lean mass than rats in the control group (FIG. 13D). The fluid mass of rats was similar across all treatment groups (FIGS. 13E and 13F).

**[0925]** FIGS. 14A and 14B show the cumulative food intake and kaolin intake of rats in Groups 1, 2, and 3. As shown in FIGS. 14A, rats that received 1 mpk E2 and 3 mpk E2 consumed less food overall after 11 days than control rats.

**[0926]** The blood glucose levels of rats in Groups 1, 2, and 3 following an oral glucose tolerance test on day 0 and through up to day 120 are shown in FIGS. 15A-15C. On day 0, blood glucose levels were substantially similar among rats in all treatment groups (FIG. 15A). In contrast, on day 8, rats in treated with 1 mpk E and 3 mpk E2 had significantly lower blood glucose levels following the oral glucose tolerance test than control rats (FIGS. 15B-15D). Notably, blood glucose levels following the oral glucose tolerance test on day 8 in rats receiving 1 mpk E2 were substantially similar to blood glucose levels of rats receiving 3 mpk E2.

**[0927]** Gastrocnemius muscle mass, and brain mass in SD rats administered saline vehicle, semaglutide (12.5/25 nmol/kg), A07D (3mpk), A07D (3mpk) + semaglutide (12.5/25 nmol/kg), semaglutide (12.5/25 nmol/kg) followed by saline alone at day 21, A07D (3mpk) followed by saline alone at day 21, A07D (3mpk) + semaglutide 12.5/25 nmol/kg) followed by A07D (3mpk) alone at day 21. Among these groups, rats administered semaglutide (12.5/25 nmol/kg), A07D (3mpk), and A07D (3mpk) + semaglutide (12.5/25 nmol/kg) each had increased muscle mass as a percent of body weight relative to saline vehicle (FIG. 16A). Rats administered semaglutide (12.5/25 nmol/kg), A07D (3mpk) + semaglutide (12.5/25 nmol/kg), and A07D (3mpk) + semaglutide 12.5/25 nmol/kg) followed by A07D (3mpk) alone each had increased brain mass (FIG. 16B) relative to saline vehicle.

**[0928]** These measurements were repeated in SD rats administered saline vehicle, tirzepatide (12.5/25 nmol/kg), A07D (3mpk), A07D (3mpk) + tirzepatide (12.5/25 nmol/kg), tirzepatide (12.5/25 nmol/kg) followed by saline alone, A07D (3mpk) followed by saline alone, A07D (3mpk) + tirzepatide 12.5/25 nmol/kg) followed by A07D (3mpk) alone.

**[0929]** Each treatment group had increased muscle mass as a percent of body weight relative to saline vehicle, albeit not statistically significant (FIG. 17A).

**[0930]** Rats administered tirzepatide (12.5/25 nmol/kg), A07D (3mpk), and A07D (3mpk) + tirzepatide (12.5/25 nmol/kg) each had increased brain mass relative to saline control, with tirzepatide (12.5/25 nmol/kg), A07D (3mpk) and A07D (3mpk) + tirzepatide (12.5/25 nmol/kg) treatment being significant (FIGS. 17B). Additionally, rats administered A07D (3mpk) + tirzepatide 12.5/25 nmol/kg followed by A07D (3mpk) alone at day 21 had increased brain mass relative to saline vehicle and rats administered tirzepatide (12.5/25 nmol/kg) followed by saline alone at day 21 or A07D (3mpk) followed by saline alone at day 21, albeit not significant.

**[0931]** Gastrocnemius muscle mass and brain mass were each measured as a percent of body weight in rats administered saline vehicle, A07D (3mpk), A07D (1mpk), A07D (3mpk) followed by saline alone at day 21, and A07D (1mpk) followed by saline alone at day 21. Among treatment groups, gastrocnemius muscle mass, liver mass, and brain mass were not statistically different from rats administered saline vehicle (FIGS. 18A and 18B).

**[0932]** Perirenal and epididymal fat mass were assessed in SD rats administered saline vehicle, semaglutide (12.5/25 nmol/kg), A07D (3mpk), A07D (3mpk) + semaglutide (12.5/25 nmol/kg), semaglutide (12.5/25 nmol/kg) followed by saline alone at day 21, A07D (3mpk) followed by saline alone at day 21, A07D (3mpk) + semaglutide 12.5/25 nmol/kg followed by A07D (3mpk) alone at day 21. Each treatment group had reduced perirenal and epididymal fat mass relative to saline control, with semaglutide (12.5/25 nmol/kg), A07D (3mpk) + semaglutide (12.5/25 nmol/kg), and A07D (3mpk) + semaglutide 12.5/25 nmol/kg followed by A07D (3mpk) alone at day 21 treated rats being significant (FIGS. 19A-19D).

**[0933]** Perirenal and epididymal fat mass were assessed in SD rats administered saline vehicle, tirzepatide (12.5/25 nmol/kg), A07D (3mpk), A07D (3mpk) + tirzepatide (12.5/25 nmol/kg), tirzepatide (12.5/25 nmol/kg) followed by saline alone at day 21, A07D (3mpk) followed by saline alone at day 21, A07D (3mpk) + tirzepatide 12.5/25 nmol/kg followed by A07D (3mpk) alone at day 21. Each treatment group had reduced perirenal fat mass relative to saline control, with tirzepatide (12.5/25 nmol/kg), A07D (3mpk) + tirzepatide (12.5/25 nmol/kg), tirzepatide (12.5/25 nmol/kg) followed by saline alone at day 21, and

A07D (3mpk) + tirzepatide 12.5/25 nmol/kg) followed by A07D (3mpk) alone treated rats being significant (FIGS. 20A and 20B). Each treatment group had reduced perirenal fat mass relative to saline control, with A07D (3mpk) + tirzepatide 12.5/25 nmol/kg) treated rats being significant (FIGS. 20C and 20D).

[0934] Perirenal and epididymal fat mass were each measured as a percentage of body weight in SD rats administered saline, A07D (3mpk), A07D (1mpk), A07D (3mpk) followed by saline alone at day 21, and A07D (1mpk) followed by saline alone at day 21. Each treatment group had reduced perirenal and epididymal fat mass relative to saline vehicle, albeit not significant (FIGS. 21A and 21B).

**Example 9: Pharmacokinetic Assessment of Non-Naturally Occurring Melanocortin Analogs Following Subcutaneous Administration to Rats**

*Study Objective*

[0935] The objective of this study is to determine the pharmacokinetics of non-naturally occurring melanocortin analogs of the present technology following subcutaneous administration in male rats. In rats, the test article will be monitored in plasma for up to 24 hours post each dose. Study design and sample collection will be conducted as outlined in Table 28 and Table 29.

Table 28. Study Design

| Animal | N | Compound | Target Dose Level | Target Dose Volume | Target Dose Concentration | Vehicle              | Dose Route |
|--------|---|----------|-------------------|--------------------|---------------------------|----------------------|------------|
|        |   |          | (mg/kg)           | (mL/kg)            | (mg/mL)                   |                      |            |
| Rat    | 3 | A07D     | 1                 | 1                  | 1                         | physiological saline | SC         |
| Rat    | 3 | A07D     | 3                 | 1                  | 3                         | physiological saline | SC         |
| Rat    | 3 | A07D     | 10                | 1                  | 10                        | physiological saline | SC         |

Table 29. Sample Collections

| Group | Dosage  | Sampling time points (hr.) |      |     |   |   |   |   |   |    |
|-------|---------|----------------------------|------|-----|---|---|---|---|---|----|
|       | (mg/kg) | 0.083                      | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 8 | 24 |
| Rat   | 1       | P                          | P    | P   | P | P | P | P | P | P  |
| Rat   | 3       | P                          | P    | P   | P | P | P | P | P | P  |

|     |    |   |   |   |   |     |     |   |   |   |
|-----|----|---|---|---|---|-----|-----|---|---|---|
| Rat | 10 | P | P | P | P | P/C | P/C | P | P | P |
|-----|----|---|---|---|---|-----|-----|---|---|---|

E: Anticoagulant: Potassium (K<sub>2</sub>) EDTA;

P: plasma

C: cerebrospinal fluid (CSF)

**[0936]** Dose Solution Analysis Samples: After each dose preparation, remove approximately 0.5 mL aliquots from the formulations, transfer the aliquots into amber HPLC vials and stored at -60°C or lower until assayed in duplicate for dose validation.

**[0937]** Disposition of Remaining Test Article Formulations: Remaining formulations will be stored at -60°C or lower.

**[0938]** Disposition of Remaining Test Article (dry powder or solid): Remaining test article will be stored at room temperature desiccated, and protected from light until shipment or discard.

**[0939]** Animals will be fasted overnight through 4 hours post dosing.

*Vehicle and Formulation Preparation:*

**[0940]** Appropriate amount of test article will be accurately weighed and mixed with appropriate volume of vehicle to get a clear solution or suspension.

**[0941]** Formulation samples will be removed from each of the formulation solutions, transferred into 1.5 mL of polypropylene microcentrifuge tubes and run dose validation by LC/UV or LC-MS/MS.

*Animal Specifications: Rats*

**[0942]** Rat specifications are outlined in Table 30.

Table 30. Rat Specifications

|             |                  |
|-------------|------------------|
| Species     | Rat              |
| Strain      | SD               |
| Source      | Approved Vendor. |
| Gender      | Male             |
| Body weight | > 200g           |

|                         |                                                                                                                                                                                                                                                                                                           |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Age                     | 7-10 W                                                                                                                                                                                                                                                                                                    |
| Total number of animals | 9 male rats                                                                                                                                                                                                                                                                                               |
| Justification           | <p>The SD rat is a standard species used in pharmacokinetic evaluations and is acceptable to regulatory agencies.</p> <p>The number of animals used in this study is, in the judgment of the investigator involved, the minimum necessary to properly perform this plasma pharmacokinetic evaluation.</p> |

#### *Observations and Examinations*

**[0943]** Clinical Observations: All animals will be observed at dosing and each scheduled collection. All abnormalities will be recorded.

**[0944]** Body Weight: All animals will be weighed on the dosing day prior to dosing to determine the dose volume to be administered.

#### *Sample Collection and Processing*

**[0945]** Blood Sample Collection and Process: At least 0.1 mL blood will be collected at each time point. All blood samples will be collected via jugular vein. All blood samples will be transferred into low binding EP tube with anticoagulant (0.5 M Potassium (K2) EDTA will be pre-added as a ratio of 50:1 for blood: anticoagulant), 0.05% Triton X-100 (e.g., 100uL Blood+2uL 2.5% Triton X-100) will be used for desorption the blood samples will be placed on wet ice.

**[0946]** Blood samples will be centrifuged within 1hr of collection at 3,200 g 4°C for 10 minutes. Following centrifugation, plasma samples will be transferred into their respective pre-labeled low binding EP tube and immediately frozen over dry ice. The plasma samples will be stored lower than -60°C until bioanalysis.

**[0947]** LC-MS/MS method development:



**[0948]** A LC-MS/MS method for the quantitative determination of test compound in biological matrix will be developed.

**[0949]** N in 1 cassette LC-MS/MS method can be developed for samples coming from different studies as long as these studies belong to the same sponsor.

**[0950]** Cassette administration assay could be performed if the mass difference ( $\Delta$ Mass) among different analytes is  $\geq 4$  Da. In this case, interference evaluation is not necessary.

**[0951]** If  $\Delta$ Mass among different analytes is less than 4 Da, there is a potential risk that interference would occur during LC-MS/MS analysis. If such kind of cassette assay is still requested by client, interference among analytes will not be evaluated but the LC separation of those analytes by using a generic method will be attempted.

**[0952]** Sample analysis:

**[0953]** A calibration curve with at least 6 non-zero calibration standards will be applied for each batch including LLOQ.

**[0954]** If sample number within a batch is  $\leq 12$ , at least one set of standard curves separated with two parts through begin and end of the sequence should be included in the run and QCs are not required. The recommended injection order is C8, C6, C4, C2, study samples, C7, C5, C3, C1.

**[0955]** If sample number within a batch is  $> 12$ , one standard curve and two sets of QCs with low, middle and high concentrations will be applied for bioanalysis. Meanwhile, QCs number should be more than 5% of study sample number.

**[0956]** Samples, coming from one client with the same type of matrix in different studies, are allowed to be quantified in one analysis run by using the developed N in 1 cassette LC-MS/MS method.

**[0957]** Acceptance criteria:

**[0958]** (1) Linearity: At least 75% of the calibration standards should fall within  $\pm 20\%$  of their nominal values for biofluid and within  $\pm 25\%$  of their nominal values for tissue and feces samples. If the endpoints, such as LLOQ and ULOQ, on the calibration curve are

eliminated, the calibration curve will be truncated. The truncated calibration curve should consist of at least 75% of the initial STDs.

**[0959]** (2) Accuracy: At least 67% of QCs should fall within  $\pm 20\%$  of their nominal values for biofluid and within  $\pm 25\%$  of their nominal values for tissue and feces samples. At least half of QCs at each concentration should be passed.

**[0960]** (3) Specificity: The mass response of analyte in the double blank and blank should be  $\leq 50\%$  LLOQ.

**[0961]** (4) Sensitivity: The LLOQ will be tried to target  $\leq 3$  ng/mL. Any adjustment of LLOQ will be informed to client in advance.

**[0962]** (5) Carryover: The mean calculated carryover peak area in the double blanks or blanks immediately after the highest standard injection should be less than that of LLOQ. If the carryover couldn't meet the criteria, the impact of the carryover on unknown samples should be re-evaluated according to the below procedure:

**[0963]** Carryover should be re-evaluated based on absolute carryover. Absolute carryover is calculated by carryover contribution multiplies carryover impact, where the carryover contribution is calculated by the area ratio of the double blank or blank with the highest carryover (Area max of carryover blank) to the ULOQ with the minimum calculated value (Area min of ULOQ), and the carryover impact is calculated by the area ratio of one injection (Area of one injection) to the following injection (Area of the following injection). The absolute carryover should be below the acceptable accuracy of the studies (e.g., 20% or 25%).

**[0964]** Carryover contribution =  $\text{Area}_{\text{max}}$  of carryover blank /  $\text{Area}_{\text{min}}$  of ULOQ  
Carryover impact =  $\text{Area of one injection} / \text{Area of the following injection}$   
Absolute carryover = Carryover contribution \* Carryover impact

#### *Data Analysis*

**[0965]** Preliminary plasma and cerebrospinal fluid (CSF) results after 24 hours of subcutaneous (SC) administration of A07D in Rats are shown in Table 31 and Table 32.

Graphs of plasma concentration and CSF concentration in Rats are shown in FIGS 22A-22D.

Table 31. Concentration of A07D in plasma and CSF of Rats over time

| Comp. Name | Dose (mg/kg) | Plasma Concentration (ng/mL) over Time |       |     |      |      |      |      |      | CSF Concentration (ng/mL) over Time |      | Plasma/CSF ratio |        |
|------------|--------------|----------------------------------------|-------|-----|------|------|------|------|------|-------------------------------------|------|------------------|--------|
|            |              | 0.25h                                  | 0.5 h | 1 h | 2 h  | 4 h  | 6 h  | 8 h  | 24 h | 2 h                                 | 4 h  | 2h               | 4 h    |
| A07D       | 1            | 228                                    | 253   | 319 | 249  | 122  | 17.1 | 1.47 | ND   | -                                   | -    | -                | -      |
| A07D       | 3            | 303                                    | 369   | 570 | 620  | 431  | 267  | 93.9 | ND   | -                                   | -    | -                | -      |
| A07D       | 10           | 274                                    | 364   | 747 | 1169 | 1139 | 844  | 575  | 7.23 | 8.60                                | 15.9 | 0.00749          | 0.0141 |

ND = not determined

Table 32. Plasma Pharmacokinetic Results of A07D in Rats after 24 hours

| Comp. Name | Dose (mg/kg) | Cmax (ng/mL) | Tmax (h) | Tfinal | T1/2 (h) | AUC <sub>0-last</sub> (ng.h/mL) | AUC <sub>0-inf</sub> (ng.h/mL) | MRT <sub>0-last</sub> (h) | MRT <sub>0-inf</sub> (h) | AUC <sub>EX</sub> (%) | AUMC <sub>EX</sub> (%) | Bioavailability (%) |
|------------|--------------|--------------|----------|--------|----------|---------------------------------|--------------------------------|---------------------------|--------------------------|-----------------------|------------------------|---------------------|
| A07D       | 1            | 319          | 1.00     | 8h-24h | 2.58     | 1066                            | 1106                           | 3.02                      | 3.87                     | 3.02                  | 14.0                   | 95.1                |
| A07D       | 3            | 647          | 1.67     | 8h     | 1.85     | 2986                            | 3305                           | 3.23                      | 3.94                     | 8.97                  | 22.3                   | 94.7                |
| A07D       | 10           | 1324         | 2.67     | 24h    | 2.50     | 9002                            | 9032                           | 5.65                      | 5.72                     | 0.319                 | 1.50                   | 77.7                |

[0966] Dose proportionality of A07D in male rats following a single subcutaneous administration in Rats is shown in Table 33.

Table 33. Dose Proportionality of A07D in Rats after a single SC administration

| Compound Name | Compare Doses (mg/kg) |      |      | Dose Ratio | Cmax Values | Cmax Ratio | AUC <sub>0-last</sub> Values | AUC <sub>0-last</sub> Ratio |
|---------------|-----------------------|------|------|------------|-------------|------------|------------------------------|-----------------------------|
| D             | 3.00                  | Over | 1.00 | 3.00       | 647/319     | 2.03       | 2986/1066                    | 2.80                        |
| D             | 10.0                  | Over | 1.00 | 3.33       | 1324/647    | 2.05       | 9002/298                     | 3.01                        |
| D             | 10.0                  | Over | 3.00 | 10.0       | 13824/319   | 4.15       | 9002/1066                    | 8.44                        |

#### **Example 10: Assessing Toxicity of Non-Naturally Occurring Melanocortin Analogs in Rats**

[0967] To assess toxicity of non-naturally occurring melanocortin analogs of the present technology, Sprague Dawley (SD) rats were assessed following subcutaneous administration of A07D.

[0968] 14 SD rats fed HFD were randomly assigned to 2 groups: Group 1 was dosed with 3 mg/kg A07D, and Group 2 was dosed with saline as a control (Tables 34 and 35). The study ran for 5 weeks, where animals were injected subcutaneously with A07D or saline

daily. A scheduled necropsy was conducted to all surviving animals at the end of study. All animals survived to the scheduled necropsy date. There were no test article-related visible macroscopic and microscopic findings in treatment animals.

Table 34: Animal Information

|                         |            |
|-------------------------|------------|
| Species                 | SD rats    |
| Number & Sex            | 14 & Males |
| Weight Range(start-end) | 130-580g   |
| Age(start-end)          | 5-14week   |

Table 35: Study Design

| Group | Number | Test Article | Dosage  | Dose Vol | Route                | Notes     |
|-------|--------|--------------|---------|----------|----------------------|-----------|
| 1     | 6      | A07D         | 3 mg/kg | 0.8-1 ml | SC<br>administration | QD*5weeks |
| 2     | 8      | Saline       | -       | 0.8-1 ml |                      | QD*5week  |

**[0969]** A complete necropsy was conducted on all animals. Gross lesion data, and organs/tissues were collected according to the study protocol. Representative samples of the liver, pancreas, heart, and adrenal glands were removed from the fixative, trimmed, processed, embedded in paraffin, sectioned, stained with hematoxylin and eosin. Histopathology evaluation was conducted on these tissues/organs by the study pathologist in a unblind-manner. Gross observations and histopathology findings are outlined in Tables 36 and 37.

Table 36: Summary of Gross Observations

|                             | Group1 | Group 2 |
|-----------------------------|--------|---------|
| Number of Animals           | 6      | 8       |
| Number of Completed Animals | 6      | 8       |
| <b>Liver</b>                |        |         |
| Submitted                   | 6      | 8       |
| No Visible Lesions          | 6      | 8       |
| <b>Pancreas</b>             |        |         |
| Submitted                   | 6      | 8       |

|                      |   |   |
|----------------------|---|---|
| No Visible Lesions   | 6 | 8 |
| <b>Heart</b>         |   |   |
| Submitted            | 6 | 8 |
| No Visible Lesions   | 6 | 8 |
| <b>Adrenal Gland</b> |   |   |
| Submitted            | 6 | 8 |
| No Visible Lesions   | 6 | 8 |

Table 37: Summary of Histopathology Observation

|                                                                      | Group1 | Group 2 |
|----------------------------------------------------------------------|--------|---------|
| Number of Animals                                                    | 6      | 8       |
| Number of Completed Animals                                          | 6      | 8       |
| <b>Liver</b>                                                         |        |         |
| Vacuolation; Hepatocyte, Periportal,<br>Diffuse                      | 0      | 2       |
| <b>Pancreas</b>                                                      |        |         |
| Fibrosis, Islet, Multifocal                                          | 1      | 5       |
| Hyperplasia, Islet cell, Multifocal                                  | 6      | 6       |
| Necrosis/Hemorrhage, Islet/Acinar<br>Cells, Multifocal               | 3      | 5       |
| Inflammation Infiltration, Interstitial,<br>Multifocal               | 1      | 3       |
| <b>Heart</b>                                                         |        |         |
| Necrosis/ Inflammation Infiltration,<br>Myocardium, Focal/Multifocal | 1      | 2       |
| <b>Adrenal Gland</b>                                                 |        |         |
| No Visible Lesions                                                   | 6      | 8       |

**[0970]** In the heart, there was minimal necrosis/ inflammation infiltration of the myocardium in Group 1 (FIG. 24B) and Group 2 (FIG. 23B). In the liver, there was minimal

vacuolation of the hepatocyte in Group 2 (FIG. 23C). In the pancreas, multifocal fibrosis, hyperplasia of the islet cells, necrosis/hemorrhage of the islet/acinar cells and inflammation infiltration of the interstitial region were observed in Group 1 (FIG. 24A) and Group 2 (FIG. 23A).

**[0971]** Considering the occurrence of lesions caused by long-term high-fat diet in saline control animals, the lesions observed in treatment animals were considered non-adverse effects. There was no unscheduled death during the study. There were no test article-related gross and histopathology findings in any treatment animals.

**Example 11: Assessing Body Weight and Food Intake After Treatment**

**[0972]** To assess changes in body weight and food intake after treatment is terminated, rats were subcutaneously administered semaglutide, tirzepatide, A07D, or saline administration according to the doses outlined in Table 38. Each compound was administered for 7 weeks, and treatment was stopped to assess body weight change (e.g., weight rebound) (FIG. 25A) and changes in food intake (FIG. 25B) in rats for the 4 weeks following termination of each treatment.

**[0973]** Statistical significance in A07D compared to saline was first observed on Day 3 of treatment, and A07D displayed similar weight loss efficacy to tirzepatide throughout the study.

**[0974]** In the final 4 weeks of the study, body weight rebound (FIG. 25C) and food intake (FIG. 25D) were again assessed when each compound was no longer administered. Rats taken off A07D had a reduced weight rebound relative to those taken off semaglutide or tirzepatide

Table 38: Dosing

| Treatment      | Dose Level (mg/kg) | Route | Frequency    | N  |
|----------------|--------------------|-------|--------------|----|
| Saline control | -                  | s.c.  | QD*7 weeks   | 8  |
| A07D           | 3                  | s.c.  | QD*7 weeks   | 10 |
| Semaglutide    | 0.051/0.103        | s.c.  | Q3D* 7 weeks | 10 |
| Tirzepatide    | 0.060/0.120        | s.c.  | Q3D*7 weeks  | 10 |

**Example 12: Residue Impact on Bioavailability**

**[0975]** To assess the impact of non-naturally occurring melanocortin analogs on bioavailability, various pharmacokinetic parameters were assessed in the plasma of male cynomolgus monkeys fasted prior to dosing A07D at 1 mg/kg intravenously, 10 mg/kg orally, or 30 mg/kg orally. Results are shown in Table 39 and FIG 26.

Table 39: A07D Results

| IV bolus1 (1 mg/kg)                  |                              |       |       |       |   |        |        |
|--------------------------------------|------------------------------|-------|-------|-------|---|--------|--------|
| Time (h)                             | C1001                        | C1002 | C1003 | Mean  |   | SD     | CV (%) |
| --                                   | Plasma Concentration (ng/mL) |       |       |       |   |        |        |
| 0.083                                | 9594                         | 5458  | 5566  | 6873  | ± | 2357   | 34.3   |
| 0.25                                 | 6334                         | 3905  | 3783  | 4674  | ± | 1439   | 30.8   |
| 0.5                                  | 5668                         | 3474  | 3125  | 4089  | ± | 1379   | 33.7   |
| 1                                    | 4917                         | 2312  | 2499  | 3243  | ± | 1453   | 44.8   |
| 2                                    | 3191                         | 1673  | 1687  | 2184  | ± | 872    | 40.0   |
| 4                                    | 1869                         | 868   | 830   | 1189  | ± | 589    | 49.6   |
| 6                                    | 1249                         | 602   | 465   | 772   | ± | 419    | 54.2   |
| 8                                    | 871                          | 324   | 238   | 478   | ± | 343    | 71.9   |
| 24                                   | 82.4                         | 17.3  | 12.6  | 37.4  | ± | 39.0   | 104    |
| PK Parameters                        | C1001                        | C1002 | C1003 | Mean  |   | SD     | CV (%) |
| Rs <sub>q</sub> _adj                 | 0.999                        | 0.995 | 0.989 | --    | ± | --     | --     |
| No. points used for T <sub>1/2</sub> | 3.00                         | 4.00  | 3.00  | ND    | ± | --     | --     |
| C <sub>0</sub> (ng/mL)               | 11793                        | 6446  | 6744  | 8328  | ± | 3005   | 36.1   |
| T <sub>1/2</sub> (h)                 | 4.63                         | 3.57  | 3.57  | 3.92  | ± | 0.612  | 15.6   |
| V <sub>dss</sub> (L/kg)              | 0.201                        | 0.328 | 0.313 | 0.281 | ± | 0.0694 | 24.7   |
| Cl(mL/min/kg)                        | 0.633                        | 1.37  | 1.48  | 1.16  | ± | 0.461  | 39.7   |
| T <sub>last</sub> (h)                | 24.0                         | 24.0  | 24.0  | 24.0  | ± | --     | --     |
| AUC <sub>0-last</sub> (ng.h/mL)      | 25795                        | 12071 | 11189 | 16352 | ± | 8190   | 50.1   |
| AUC <sub>0-inf</sub> (ng.h/mL)       | 26346                        | 12160 | 11254 | 16587 | ± | 8464   | 51.0   |
| MRT <sub>0-last</sub> (h)            | 4.76                         | 3.81  | 3.37  | 3.98  | ± | 0.710  | 17.8   |
| MRT <sub>0-inf</sub> (h)             | 5.31                         | 3.99  | 3.52  | 4.27  | ± | 0.928  | 21.7   |
| AUC <sub>Extra</sub> (%)             | 2.09                         | 0.733 | 0.577 | 1.13  | ± | 0.832  | 73.4   |
| AUMC <sub>Extra</sub> (%)            | 12.1                         | 5.35  | 4.78  | 7.41  | ± | 4.07   | 54.9   |
| PO2 (10 mg/kg)                       |                              |       |       |       |   |        |        |
| Time (h)                             | C2001                        | C2002 | C2003 | Mean  |   | SD     | CV (%) |
| --                                   | Plasma Concentration (ng/mL) |       |       |       |   |        |        |
| 0.083                                | 2.85                         | 3.83  | 8.58  | 5.09  | ± | 3.06   | 60.3   |
| 0.25                                 | 20.2                         | 101   | 23.2  | 48.1  | ± | 45.8   | 95.2   |
| 0.5                                  | 67.0                         | 418   | 74.9  | 187   | ± | 200    | 107    |
| 1                                    | 85.1                         | 450   | 111   | 215   | ± | 204    | 94.5   |
| 2                                    | 174                          | 408   | 79.6  | 221   | ± | 169    | 76.7   |

|                                      |                              |       |       |       |    |       |        |
|--------------------------------------|------------------------------|-------|-------|-------|----|-------|--------|
| 4                                    | 136                          | 240   | 59.8  | 145   | ±  | 90.5  | 62.3   |
| 6                                    | 90.9                         | 171   | 45.3  | 102   | ±  | 63.6  | 62.1   |
| 8                                    | 53.7                         | 71.5  | 23.2  | 49.5  | ±  | 24.4  | 49.4   |
| 24                                   | 8.75                         | 7.42  | 2.45  | 6.21  | ±  | 3.32  | 53.5   |
| PK Parameters                        | C2001                        | C2002 | C2003 | Mean  |    | SD    | CV (%) |
| Rsq_adj                              | 0.974                        | 0.963 | 0.987 | --    | ±  | --    | --     |
| No. points used for T <sub>1/2</sub> | 3.00                         | 5.00  | 5.00  | ND    | ±  | --    | --     |
| C <sub>max</sub> (ng/mL)             | 174                          | 450   | 111   | 245   | ±  | 180   | 73.6   |
| T <sub>max</sub> (h)                 | 2.00                         | 1.00  | 1.00  | 1.33  | ±  | 0.577 | 43.3   |
| T <sub>1/2</sub> (h)                 | 5.61                         | 3.93  | 4.37  | 4.64  | ±  | 0.871 | 18.8   |
| T <sub>last</sub> (h)                | 24.0                         | 24.0  | 24.0  | 24.0  | ±  | --    | --     |
| AUC <sub>0-last</sub> (ng.h/mL)      | 1251                         | 2441  | 613   | 1435  | ±  | 928   | 64.7   |
| AUC <sub>0-inf</sub> (ng.h/mL)       | 1321                         | 2483  | 628   | 1477  | ±  | 937   | 63.4   |
| MRT <sub>0-last</sub> (h)            | 6.94                         | 5.01  | 5.74  | 5.90  | ±  | 0.974 | 16.5   |
| MRT <sub>0-inf</sub> (h)             | 8.29                         | 5.43  | 6.34  | 6.69  | ±  | 1.46  | 21.9   |
| AUC <sub>Extra</sub> (%)             | 5.36                         | 1.69  | 2.46  | 3.17  | ±  | 1.94  | 61.0   |
| AUMC <sub>Extra</sub> (%)            | 20.7                         | 9.24  | 11.7  | 13.9  | ±  | 6.03  | 43.5   |
| Bioavailability (%) <sup>a</sup>     | -                            | -     | -     | 0.890 | -- | --    | --     |
| PO3 (30 mg/kg)                       |                              |       |       |       |    |       |        |
| Time (h)                             | C3001                        | C3002 | C3003 | Mean  |    | SD    | CV (%) |
| --                                   | Plasma Concentration (ng/mL) |       |       |       |    |       |        |
| 0.083                                | 17.0                         | 10.4  | 33.8  | 20.4  | ±  | 12.1  | 59.1   |
| 0.25                                 | 108                          | 24.0  | 97.6  | 76.5  | ±  | 45.8  | 59.8   |
| 0.5                                  | 431                          | 37.3  | 171   | 213   | ±  | 200   | 93.9   |
| 1                                    | 504                          | 122   | 236   | 287   | ±  | 196   | 68.3   |
| 2                                    | 502                          | 427   | 326   | 418   | ±  | 88.3  | 21.1   |
| 4                                    | 332                          | 320   | 244   | 299   | ±  | 47.7  | 16.0   |
| 6                                    | 220                          | 190   | 180   | 197   | ±  | 20.8  | 10.6   |
| 8                                    | 120                          | 124   | 163   | 136   | ±  | 23.8  | 17.5   |
| 24                                   | 57.7                         | 19.1  | 39.6  | 38.8  | ±  | 19.3  | 49.8   |
| PK Parameters                        | C3001                        | C3002 | C3003 | Mean  |    | SD    | CV (%) |
| Rsq_adj                              | 0.785                        | 0.989 | 0.996 | --    | ±  | --    | --     |
| No. points used for T <sub>1/2</sub> | 5.00                         | 3.00  | 3.00  | ND    | ±  | --    | --     |
| C <sub>max</sub> (ng/mL)             | 504                          | 427   | 326   | 419   | ±  | 89.3  | 21.3   |
| T <sub>max</sub> (h)                 | 1.00                         | 2.00  | 2.00  | 1.67  | ±  | 0.577 | 34.6   |
| T <sub>1/2</sub> (h)                 | 7.80                         | 5.61  | 8.08  | 7.16  | ±  | 1.35  | 18.9   |
| T <sub>last</sub> (h)                | 24.0                         | 24.0  | 24.0  | 24.0  | ±  | --    | --     |
| AUC <sub>0-last</sub> (ng.h/mL)      | 3873                         | 2772  | 3154  | 3266  | ±  | 559   | 17.1   |
| AUC <sub>0-inf</sub> (ng.h/mL)       | 4522                         | 2927  | 3615  | 3688  | ±  | 800   | 21.7   |
| MRT <sub>0-last</sub> (h)            | 7.44                         | 7.05  | 8.39  | 7.63  | ±  | 0.689 | 9.04   |
| MRT <sub>0-inf</sub> (h)             | 11.4                         | 8.37  | 11.9  | 10.6  | ±  | 1.91  | 18.1   |



|                                  |      |      |      |       |    |      |      |
|----------------------------------|------|------|------|-------|----|------|------|
| AUC <sub>Extra</sub> (%)         | 14.4 | 5.28 | 12.8 | 10.8  | ±  | 4.87 | 45.0 |
| AUMC <sub>Extra</sub> (%)        | 44.3 | 20.2 | 38.4 | 34.3  | ±  | 12.6 | 36.6 |
| Bioavailability (%) <sup>a</sup> | -    | -    | -    | 0.741 | -- | --   | --   |

[0976] ND = Not determined (Parameters not determined due to inadequately defined terminal elimination phase).

[0977] BQL = Below the lower limit of quantitation (LLOQ).

[0978] If the adjusted rsq (linear regression coefficient of the concentration value on the terminal phase) is less than 0.9, T<sub>1/2</sub> might not be accurately estimated.

[0979] If the % AUC<sub>Extra</sub> > 20%, AUC<sub>0-inf</sub>, CI, MRT<sub>0-inf</sub> and Vd<sub>ss</sub> might not be accurately estimated.

[0980] If the % AUMC<sub>Extra</sub> > 20%, MRT<sub>0-inf</sub> and Vd<sub>ss</sub> might not be accurately estimated.

[0981] The adjusted linear regression coefficient of the concentration value on the terminal phase is less than 0.9, T<sub>1/2</sub> might not be accurately estimated.

[0982] a: Bioavailability (%) was calculated using AUC<sub>0-inf</sub> (if all AUC<sub>Extra</sub> ≤ 20%) or AUC<sub>0-last</sub> (if one or more AUC<sub>Extra</sub> > 20%) with Nominal Dose.

### **Additional Embodiments**

[0983] Various embodiments of the present technology are set forth below in paragraphs [0984] to [1183]:

[0984] 1. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising administering to the subject:

(a) a GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog, to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject.

[0985] 2. Use of (a) a non-naturally occurring melanocortin analog and (b) a GLP-1 receptor agonist for reducing body weight and/or fat mass in a subject in need thereof to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject.

[0986] 3. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising administering to the subject:

a non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

**[0987]** 4. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

**[0988]** 5. The method or the use of any one of embodiments 1-4, wherein the method further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

**[0989]** 6. The method of the use of embodiment 5, wherein the lean mass is lean muscle mass.

**[0990]** 7. The method or the use of any one of embodiments 1 to 6, wherein the method further comprises treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in the subject.

**[0991]** 8. A method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising administering to the subject:

(a) a GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog, to produce a synergistic or additive effect on glucose intolerance and/or diabetes mellitus in the subject.

**[0992]** 9. Use of (a) a non-naturally occurring melanocortin analog and (b) a GLP-1 receptor agonist for treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof to produce a synergistic or additive effect on glucose intolerance and/or diabetes mellitus in the subject

**[0993]** 10. A method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising administering to the subject:

a non-naturally occurring melanocortin analog comprising a sequence of Formula:

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

**[0994]** 11. Use of a non-naturally occurring melanocortin analog for treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidinyloxyproline (cisPro(guan)), and trans-4-guanidinyloxyproline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

**[0995]** a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

**[0996]** 12. The method or the use of any one of embodiments 8-11, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

**[0997]** 13. The method or the use of embodiment 12, wherein the lean mass is lean muscle mass.



- [0998]** 14. The method or the use of any one of embodiments 8 to 13, wherein the method or the use further comprises reducing body weight and/or fat mass in the subject.
- [0999]** 15. The method or the use of any one of embodiments 8 to 14, wherein the method or the use further comprises treating, preventing, reducing, or otherwise ameliorating a sleep disorder in the subject.
- [1000]** 16. The method or the use of embodiment 15, wherein the sleep disorder is sleep apnea.
- [1001]** 17. The method or the use of any one of embodiments 1 to 14, wherein the GLP-1 receptor agonist is administered at a dose that is less than a dose required to elicit a response in the subject without the non-naturally occurring melanocortin analog.
- [1002]** 18. The method or the use of any one of embodiments 1 to 15, wherein the non-naturally occurring melanocortin analog is administered at a dose that is less than a dose required to elicit a response in the subject without the GLP-1 receptor agonist or the dual GLP-1/GIP receptor agonist.
- [1003]** 19. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 0.01 mg to about 10 mg once per week.
- [1004]** 20. The method or the use of embodiment 19, wherein semaglutide is administered subcutaneously at a dose of less than 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week.
- [1005]** 21. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 0.5 mg to about 40 mg once daily.
- [1006]** 22. The method or the use of embodiment 21, wherein semaglutide is administered orally at a dose of less than 3 mg, 7 mg or 14 mg once daily.
- [1007]** 23. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 12.5 nmol/kg or 25 nmol/kg per body weight of the subject once every three days.

**[1008]** 24. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is exenatide and is administered at a dose of about 0.5 µg to about 100 µg twice daily.

**[1009]** 25. The method or the use of embodiment 24, wherein exenatide is administered subcutaneously at a dose of less than 5 µg or 10 µg twice daily.

**[1010]** 26. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is exenatide and is administered at a dose of about 0.5 mg to about 50 mg once per week.

**[1011]** 27. The method or the use of embodiment 26, wherein exenatide is administered subcutaneously at a dose of less than 2 mg once per week.

**[1012]** 28. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is dulaglutide and is administered at a dose of about 0.05 mg to about 50 mg once per week.

**[1013]** 29. The method or the use of embodiment 28, wherein dulaglutide is administered subcutaneously at a dose of less than 0.75 mg, 1.5 mg, 3.0 mg or 4.5 mg once per week.

**[1014]** 30. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is orforglipron and is administered at a dose of about 0.01 mg to about 100 mg once daily.

**[1015]** 31. The method or the use of embodiment 30, wherein orforglipron is administered orally at a dose of less than 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, or 24 mg once daily.

**[1016]** 32. The method or the use of any one of embodiments 1 to 16, wherein the GLP-1 receptor agonist is a dual GLP-1/GIP receptor agonist.

**[1017]** 33. The method or the use of embodiment 32, wherein the dual GIP/GLP-1 receptor agonist is tirzepatide and is administered at a dose of about 0.5 mg to about 50 mg once per week.

**[1018]** 34. The method or the use of embodiment 33, wherein tirzepatide is administered subcutaneously at a dose of less than 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg once per week.

**[1019]** 35. The method or the use of embodiment 32, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and is administered at a dose of about 12.5 nmol/kg or 25 nmol/kg per body weight of the subject once every three days.

**[1020]** 36. The method or the use of any one of embodiments 1 to 33, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.5 mg/kg to about 10 mg/kg per body weight of the subject once daily.

**[1021]** 37. The method or the use of embodiment 36, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 1 mg/kg or 3 mg/kg per body weight of the subject once daily.

**[1022]** 38. The method or the use of any one of embodiments 1 to 33, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

**[1023]** 39. The method or the use of any one of embodiments 1 to 33, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

**[1024]** 40. The method or the use of any one of embodiments 1 to 37, wherein the melanocortin 4 receptor agonist is an agonist of the melanocortin 3 receptor.

**[1025]** 41. The method or the use of embodiment 40, wherein the melanocortin 4 receptor agonist is a full agonist of the melanocortin 3 receptor.

**[1026]** 42. The method or the use of embodiment 40 or 41, wherein the non-naturally occurring melanocortin agonist comprises no melanocortin 3 receptor antagonist activity.

**[1027]** 43. The method or the use of any one of embodiments 1 to 42, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to administration of the GLP-1 receptor agonist, and wherein administration of the non-

naturally occurring melanocortin analog makes the subject more responsive to the GLP-1 receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin 4 receptor analog.

**[1028]** 44. The method or the use of any one of embodiments 1 to 42, wherein the non-naturally occurring melanocortin agonist is administered to the subject after administration of the GLP-1 receptor agonist, and wherein the subject failed to lose sufficient body weight and/or fat mass following administration with the GLP-1 receptor agonist without the non-naturally occurring melanocortin analog.

**[1029]** 45. The method or the use of embodiment 44, wherein the non-naturally occurring melanocortin analog is administered to the subject after administration of the GLP-1 receptor agonist for one dose, one week, or one cycle.

**[1030]** 46. The method or the use of embodiment 44, wherein the non-naturally occurring melanocortin analog is administered to the subject after treatment with the GLP-1 receptor agonist is complete.

**[1031]** 47. The method or the use of any one of embodiments 1 to 42, wherein the GLP-1 receptor agonist is administered to the subject for a period of time before administration of the non-naturally occurring melanocortin analog, and wherein, while the non-naturally occurring melanocortin analog is administered to the subject, administration of the GLP-1 receptor agonist is paused, and wherein, when administration of the non-naturally occurring melanocortin analog is completed, administration of the GLP-1 receptor agonist is resumed.

**[1032]** 48. The method or the use of any one of embodiments 1 to 42, wherein the non-naturally occurring melanocortin analog is administered to the subject for a period of time before administration of the GLP-1 receptor agonist, and wherein, while the non-GLP-1 receptor agonist is administered to the subject, administration of the non-naturally occurring melanocortin analog is paused, and wherein, when administration of the GLP-1 receptor agonist is completed, administration of the non-naturally occurring melanocortin analog is resumed.

**[1033]** 49. The method or the use of any one of embodiments 1 to 46, wherein the method or the use further comprises preventing or reducing one or more side effects associated with the GLP-1 receptor agonist.

**[1034]** 50. The method or the use of embodiment 49, wherein the one or more side effects associated with the GLP-1 receptor agonist is a gastrointestinal effect.

**[1035]** 51. The method or the use of embodiment 50, wherein the gastrointestinal effect is one or more of nausea, vomiting, and diarrhea.

**[1036]** 52. The method or the use of any one of embodiments 49 to 47, wherein the one or more side effects associated with the GLP-1 receptor agonist is an adverse cardiovascular event.

**[1037]** 53. The method or the use of embodiment 52, wherein the adverse cardiovascular event is one or more of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, and peripheral vascular disease.

**[1038]** 54. The method or the use of any one of embodiments 1 to 51, wherein the method or the use further comprises preventing or reducing one or more side effects associated with the non-naturally occurring melanocortin analog.

**[1039]** 55. The method or the use of any one of embodiments 54, wherein the one or more side effects associated with the non-naturally occurring melanocortin analog is an adverse cardiovascular event.

**[1040]** 56. The method or the use of embodiment 55, wherein the adverse cardiovascular event is sinus tachycardia.

**[1041]** 57. The method or the use of any one of embodiments 1 to 54, wherein the method or the use further comprises reducing obesity-related inflammation in the subject.

**[1042]** 58. The method or the use of any one of embodiments 1 to 55, wherein the method or the use further comprises preserving or improving kidney function in the subject.

**[1043]** 59. A method of treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with the use of a GLP-1 receptor agonist in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the GLP-1 receptor agonist.

**[1044]** 60. Use of a non-naturally occurring melanocortin receptor agonist for treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with the use of a GLP-1 receptor agonist in a subject, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to, during, and/or after administration of the GLP-1 receptor agonist.

**[1045]** 61. The method or the use of embodiment 59 or 60, wherein the GLP-1 receptor is administered at a dose sufficient to elicit weight loss in the subject, and wherein the dose sufficient to elicit weight loss in the subject is lower than a dose of the GLP-1 receptor agonist required to elicit weight loss in the subject without the non-naturally occurring melanocortin analog.

**[1046]** 62. The method or the use of any one of embodiments 59-61, wherein the one or more side effects associated with the use of a GLP-1 receptor agonist is an adverse cardiovascular event.

**[1047]** 63. The method or the use of embodiment 62, wherein the adverse cardiovascular event is one or more of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, and peripheral vascular disease.

**[1048]** 64. The method or the use of any one of embodiments 59-61, wherein the one or more side effects associated with the use of the GLP-1 receptor agonist is a gastrointestinal effect.

**[1049]** 65. The method or the use of embodiment 64, wherein the gastrointestinal effect is one or more of nausea, vomiting, and diarrhea.

**[1050]** 66. A method of reducing obesity-related inflammation in a subject in need thereof, comprising administering to the subject:

- (a) a GLP-1 receptor agonist; and
- (b) a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist

**[1051]** 67. Use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for reducing obesity-related inflammation in a subject in need thereof, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

**[1052]** 68. A method of reducing obesity-related inflammation in a subject in need thereof, comprising administering to the subject a non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

69. Use of a non-naturally occurring melanocortin analog for reducing obesity-related inflammation in a subject in need thereof, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:



X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidinyI-proline (cisPro(guan)), and trans-4-guanidinyI-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

**[1053]** a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;  
provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

**[1054]** 70. A method of preserving or improving kidney function in a subject in need thereof, comprising administering to the subject:

(a) a GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

**[1055]** 71. Use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for preserving or improving kidney function in a subject in need thereof, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

**[1056]** 72. A method of preserving or improving kidney function in a subject in need thereof, comprising administering to the subject:

a non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

**[1057]** 73. Use of a non-naturally occurring melanocortin analog for preserving or improving kidney function in a subject in need thereof, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

**[1058]** a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

**[1059]** a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys a R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

**[1060]** 74. The method or the use of any one of embodiments 1 to 73, wherein the subject has a metabolic dysfunction selected from the group consisting of obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies.

**[1061]** 75. The method or the use of any one of embodiments 1-74, wherein the method or the use increases tolerance for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[1062]** 76. The method or the use of embodiment 75, wherein the increased tolerance comprises reduced nausea.

**[1063]** 77. The method or the use of any one of embodiments 1-76, wherein the method or the use maintains or increases a muscle mass level relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[1064]** 78. The method or the use of embodiment 77, wherein the muscle mass comprises lean muscle mass.

**[1065]** 79. The method or the use of any one of embodiments 1-78, wherein the method or the use increases a preference level or a compliance level for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[1066]** 80. The method or the use of any one of embodiments 1-79, wherein the method or the use comprises increasing a weight loss level for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[1067]** 81. The method or the use of any one of embodiments 1-80, wherein the method or the use comprises a reduction in one or more side effects associated with the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[1068]** 82. The method or the use of any one of embodiments 1-81, wherein the method or the use comprises reducing a weight loss plateau for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[1069]** 83. The method or the use of any one of embodiments 1-82, wherein the method or the use reduces an appetite level or a weight gain level relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

**[1070]** 84. The method or the use of any one of embodiments 1-83, wherein the method or the use does not reduce efficacy of the GLP-1 receptor agonist relative to a control.

**[1071]** 85. The method or the use of any one of embodiments 1-83, wherein the method or the use increases efficacy of the GLP-1 receptor agonist relative to a control.

**[1072]** 86. The method or the use of any one of embodiments 1-83, wherein the method or the use does not plateau body weight loss in the subject.

**[1073]** 87. The method or the use of any one of embodiments 1-83, wherein the method or the use does not plateau fat mass loss in the subject.

**[1074]** 88. The method or the use of any one of embodiments 1-87, wherein the method or the use prevents fat mass gain after administration of the GLP-1 receptor agonist relative to a control.

**[1075]** 89. The method or the use of any one of embodiments 1-88, wherein the method or the use prevents body weight gain after administration of the GLP-1 receptor agonist relative to a control.

**[1076]** 90. The method or the use of any one of embodiments 1-88, wherein the method or the use reduces body weight gain after administration of the GLP-1 receptor agonist relative to a control.

**[1077]** 91. The method or the use of any one of embodiments 1-88, wherein the method or the use reduces fat mass gain after administration of the GLP-1 receptor agonist relative to a control.

**[1078]** 92. The method or the use of any one of embodiments 1-91, wherein the method or the use reduces a blood sugar level in the subject relative to a control.

**[1079]** 93. The method or the use of any one of embodiments 1-91, wherein the method or the use prevents a blood sugar elevation in the subject after administration of the GLP-1 receptor agonist relative to a control.

**[1080]** 94. The method or the use of any one of embodiments 1-91, wherein the method or the use reduces a blood sugar elevation in the subject after administration of the GLP-1 receptor agonist relative to a control.

**[1081]** 95. The method or the use of any one of embodiments 1-94, wherein the method or the use maintains or increases brain mass in the subject during or after administration of the GLP-1 receptor agonist relative to a control.

**[1082]** 96. The method or the use of any one of embodiments 1-94, wherein the method or the use prevents or reduces brain mass loss in the subject during or after administration of the GLP-1 receptor agonist relative to a control.

**[1083]** 97. The method or the use of any one of embodiments 1-96, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I):

X1-R1-R2-R3-R4-R5-R6-R7-R8-R9-Y1-Y2-Y3-Y4 (I),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidinyI-proline (cisPro(guan)), and trans-4-guanidinyI-proline (transPro(guan));



R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

**[1084]** Y4 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

**[1085]** a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

**[1086]** a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that:

when one or both of R2 and R3 is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R1 and Lys at R9;

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present and Y4 is absent, or (ii) X1, Y3, and Y4 are absent, R1 is Nle, R4 is dPhe, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated; and

when R2 is Ala, then X1 is Nle.

98. The method or the use of any one of embodiments 1-96, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I), wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R4 is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidinyI-proline (cisPro(guan)), and trans-4-guanidinyI-proline (transPro(guan));

R6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R7 is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R8 is absent, Lys, or Trp;

R9 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

**[1087]** a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys;

**[1088]** a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 or R8 is Lys; and

**[1089]** a lactam bridge between R1 and R9 when R1 is Asp, R6 is dPhe, and R9 is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac-Nle-c[Asp-Phe-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 366);

Ac-Nle-c[Asp-Phe-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 412);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 423);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 424);

Ac-Nle-c[Asp-Phe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 487);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 225);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231);

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302);

His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 306);

dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 309);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 311);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 312);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 313);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 314);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 315);

Ac-Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 413);  
Ac-Nle-c[Asp-dHis-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 416);  
Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 425);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436);  
Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 437);  
Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 438);  
Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 439);  
Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 440);  
Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 441);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 443);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 447);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453);  
Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 454);  
Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 455);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 456);  
Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 457);  
Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 458);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 597);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 598);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641);  
Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 642);  
Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 643);  
Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 644);  
Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 645);  
Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 646);  
Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); and  
Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[1090]** 99. The method or the use of any one of embodiments 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IA):

X1-R1-R2-R3-R4-R5-R6-R7-R8-Y1-Y2-Y3-Y4 (IA),

wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, Ala, and D-alanine (dAla);

R3 is His or dHis;

R4 is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R5 is His or Arg;

R6 is tryptophan (Trp);

R7 is Pro or lysine (Lys);

R8 is absent or lysine (Lys);

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is dVal or dPro;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp and R7 or R8 is Lys;

provided that when R2 is Ala, then X1 is Nle.

**[1091]** 100. The method or the use of any one of embodiments 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IA), wherein:

X1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R1 is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is selected from the group consisting of Asp, Ala, and D-alanine (dAla);

R3 is His or dHis;

R4 is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R5 is His or Arg;

R6 is tryptophan (Trp);

R7 is Pro or lysine (Lys);

R8 is absent or lysine (Lys);

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is dVal or dPro;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp and R7 or R8 is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise the sequence:

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[1092]** 101. The method or the use of any one of embodiments 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IB):

X1-R1-R2-His-R4-R5-R6-R7-R8-Y1-Y2-Y3-Y4 (IB),

wherein:

X1 is absent or is norleucine (Nle);

R1 is selected from the group consisting of Nle, Arg, dArg, alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is Asp;

R4 is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R5 is selected from the group consisting of His, Arg, cis-4-guanidinyI-proline (cisPro(guan)), and trans-4-guanidinyI-proline (transPro(guan));

R6 is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R7 is Pro or Lys;

R8 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R2 and R7 or R8 when R2 is Asp, and R7 or R8 is Lys.

**[1093]** 102. The method or the use of embodiment 101, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IB), wherein:

X1 is absent or is norleucine (Nle);



R1 is selected from the group consisting of Nle, Arg, lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R2 is Asp;

R4 is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R5 is His or Arg;

R6 is tryptophan (Trp);

R7 is Pro or Lys;

R8 is absent or Lys;

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is dVal or dPro;

Y3 is absent, dVal, or dPro;

Y4 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R2 and R7 or R8 when R2 is Asp, and R7 or R8 is Lys.

**[1094]** 103. The method or the use of any one of embodiments 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IC):

X1-R1-R2-His-R4-R5-R6-R7-Y1-Y2 (IC),

wherein:

X1 is norleucine (Nle), arginine (Arg) or D-arginine (dArg);

R1 is aspartic acid (Asp);

R2 is alanine (Ala) or D-alanine (dAla);

R4 is D-phenylalanine (dPhe);

R5 is Arg;

R6 is tryptophan (Trp);

R7 is Lys;

Y1 is D-valine (dVal);

Y2 is D-proline (dPro); and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R2 and Lys at R7;

provided that when R2 is Ala, then X1 is Nle.

**[1095]** 104. The method or the use of any one of embodiments 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IC), wherein:

X1 is norleucine (Nle), arginine (Arg) or D-arginine (dArg);

R1 is aspartic acid (Asp);

R2 is alanine (Ala) or D-alanine (dAla);

R4 is D-phenylalanine (dPhe);

R5 is Arg;

R6 is tryptophan (Trp);

R7 is Lys;

Y1 is D-valine (dVal);

Y2 is D-proline (dPro); and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R2 and Lys at R7;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence of:

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

**[1096]** 105. The method or the use of any one of embodiments 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (ID):

X1-R1-R2-R3-R4-R5-R6-R7-Y1-Y2-Y3 (ID),

wherein:

X1 is absent or is norleucine (Nle);

R1 is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro);

R3 is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro);

R4 is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R7 is cysteine (Cys) or lysine (Lys);

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; and

a lactam bridge between R1 or R2 and R7 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe, and R7 is Lys;

provided that:

when R3 is Pro, then R4 is dPhe and either (i) X1 and Y3 are present, or (ii) X1 and Y3 are absent, R1 is Nle, R5 is Arg, R6 is Trp, Y1Y2 is dVal-dPro, and the C-terminus is amidated;

when R4 is dPhe, then (i) R3 is not His or Gln or (ii) R3 is His and either R2 is Pro or R5 is transPro(guan) or cisPro(guan); and

when R4 is p(F)dPhe, R3 is His, and R1 is Nle, then (i) R6 is not Trp or (ii) Y3 is dVal.

**[1097]** 106. The method or the use of any one of embodiments 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (ID), wherein:

X1 is absent or is norleucine (Nle);

R1 is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala);

R2 is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro);

R3 is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro);

R4 is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R5 is selected from the group consisting of Arg, cis-4-guanidiny-proline (cisPro(guan)), and trans-4-guanidiny-proline (transPro(guan));

R6 is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R7 is cysteine (Cys) or lysine (Lys);

Y1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y2 is selected from the group consisting of dVal, dPro, and dTle;

Y3 is absent, dVal, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R2 and R7 when R2 is dCys, R4 is p(Cl)dPhe, and R7 is Cys; and  
a lactam bridge between R1 or R2 and R7 when R1 or R2 is Asp, R4 is dPhe or p(F)dPhe,  
and R7 is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise a  
sequence selected from the group consisting of:

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218);  
Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 225);  
Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231);  
Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641);  
Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363);  
Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370);  
Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621);  
Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223);  
Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469);  
Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475);  
Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and  
Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478).

**[1098]** 107. The method or the use of any one of embodiments 3-106, wherein an N-terminus of the non-naturally occurring melanocortin analog, if present, is modified by an acyl group.

**[1099]** 108. The method or the use of embodiment 107, wherein the acyl group is an acetyl group.

**[1100]** 109. The method or the use of any one of embodiments 3-106, wherein an N-terminus of the non-naturally occurring melanocortin analog, if present, is not modified.

**[1101]** 110. The method or the use of any one of embodiments 3-109, wherein a C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group.

**[1102]** 111. The method or the use of any one of embodiments 3-109, wherein a C-terminus of the non-naturally occurring melanocortin analog is not modified.

**[1103]** 112. The method or the use of any one of embodiments 3-111, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond.

**[1104]** 113. The method or the use of any one of embodiments 3-112, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R2 and R7.

**[1105]** 114. The method or the use of any one of embodiments 3-113, wherein R4 is dPhe or p(F)dPhe.

**[1106]** 115. The method or the use of any one of embodiments 3-114, wherein R3 is His.

**[1107]** 116. The method or the use of any one of embodiments 3-115, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 476);

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363); and

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621),

wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1108]** 117. The method or the use of any one of embodiments 3-115, wherein R4 is p(F)dPhe.

**[1109]** 118. The method or the use of embodiment 117, wherein R1 is selected from the group consisting of Ala, Arg, dArg, Lys, dLys, His, and dHis.

**[1110]** 119. The method or the use of embodiment 117 or 118, wherein Y1 is dVal and Y2 is dPro.

**[1111]** 120. The method or the use of any one of embodiments 3-115 and 117-119, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 462);

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 463);

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 464);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 465);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 466);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 467); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 468),

wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1112]** 121. The method or the use of embodiment 117 or 118, wherein Y1 is dTle and Y2 is dPro.

**[1113]** 122. The method or the use of any one of embodiments 3-115, 117, 118, and 121, wherein the sequence according of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 479);

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 480);

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 481);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 482);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 483);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 484); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 485),



wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1114]** 123. The method or the use of any one of embodiments 3-115, wherein R4 is p(F)dPhe.

**[1115]** 124. The method or the use of embodiment 123, wherein at least one of X1, Y3, and Y4 is present.

**[1116]** 125. The method or the use of any one of embodiments 3-115, 124, and 123, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 469);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH2 (SEQ ID NO: 473);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH2 (SEQ ID NO: 474);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH2 (SEQ ID NO: 475);

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH2 (SEQ ID NO: 477); and

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH2 (SEQ ID NO: 478),

wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1117]** 126. The method or the use of any one of embodiments 3-115, wherein R5 is selected from the group consisting of His, transPro(guan) and cisPro(gaun).

**[1118]** 127. The method or the use of any one of embodiments 3-115 and 126, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-His-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 228);

Ac-Nle-c[Asp-His-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 229); and

Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 470),

wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1119]** 128. The method or the use of any one of embodiments 3-115, wherein R6 is dNal(2').

**[1120]** 129. The method or the use of any one of embodiments 3-115 and 128, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 471), wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1121]** 130. The method or the use of any one of embodiments 3-114, wherein R3 is not His.

**[1122]** 131. The method or the use of any one of embodiments 3-114 and 130, wherein R3 is selected from the group consisting of dHis, Gln, and Pro.

**[1123]** 132. The method or the use of any one of embodiments 3-115, 130, and 131, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 365);

Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370);

Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 486);

Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 491); and

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 639),

wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1124]** 133. The method or the use of any one of embodiments 3-112, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R1 and R7 or R2 and R8.

**[1125]** 134. The method or the use of any one of embodiments 3-112 and 133, wherein R4 is dPhe.

**[1126]** 135. The method or the use of any one of embodiments 3-112, 133, and 134, wherein R3 is His.

**[1127]** 136. The method or the use of any one of embodiments 3-112 and 133-135, wherein X1 and R1 are present.

**[1128]** 137. The method or the use of any one of embodiments 3-112 and 133-136, wherein R2 is Ala or dAla.

**[1129]** 138. The method or the use of any one of embodiments 3-112 and 133-137, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 268);

Ac-Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 378);

Ac-dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 379); and

Ac-Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 380),

wherein c represents cyclization through R1 and R7 via a lactam bond.

**[1130]** 139. The method or the use of any one of embodiments 3-112 and 133-135, wherein either R2 or R7 is Pro.

**[1131]** 140. The method or the use of any one of embodiments 3-112, 133-135, and 139, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 297); or

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 418).

wherein c represents cyclization through R2 and R7 via a lactam bond.

**[1132]** 141. The method or the use of any one of embodiments 3-112, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R1 and R9.

**[1133]** 142. The method or the use of any one of embodiments 3-112 and 141, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 420), wherein c represents cyclization through R1 and R9 via a lactam bond.

**[1134]** 143. The method or the use of any one of embodiments 3-111, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a disulfide bond.

**[1135]** 144. The method or the use of any one of embodiments 3-111 and 142, wherein R4 is p(Cl)dPhe.

**[1136]** 145. The method or the use of any one of embodiments 3-111, 142, and 143, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 498), wherein c represents cyclization through R2 and R7 via a disulfide bond.

**[1137]** 146. The method or the use of any one of embodiments 1-96, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498.

**[1138]** 147. The method or the use of embodiment 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486.

**[1139]** 148. The method or the use of embodiment 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621.

**[1140]** 149. The method or the use of embodiment 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621.

**[1141]** 150. The method or the use of embodiment 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 268 and 378-380.

**[1142]** 151. The method or the use of embodiment 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

**[1143]** 152. The method or the use of any one of embodiments 1-151, wherein the GLP-1 receptor agonist is present in a first pharmaceutical composition.

**[1144]** 153. The method or the use of embodiment 152, wherein the first pharmaceutical composition comprises one or more pharmaceutically acceptable excipients and/or carriers.

**[1145]** 154. The method or the use of embodiment 153, wherein the one or more pharmaceutically acceptable excipients and/or carriers of the first pharmaceutical composition comprise water.

**[1146]** 155. The method or the use of any one of embodiments 152-154, wherein the GLP-1 receptor agonist is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[1147]** 156. The method or the use of embodiment 155, wherein the GLP-1 receptor agonist is semaglutide and is present in the first pharmaceutical composition in a concentration of 0.5 mg/mL to 5.0 mg/mL, 0.5 mg/mL to 4.0 mg/mL, 0.6 mg/mL to 3.5 mg/mL, 0.65 mg/mL to 3.2 mg/mL, 0.65 mg/mL to 3.0 mg/mL, 0.8 mg/mL to 2.8 mg/mL, 1.0 mg/mL to 3.0 mg/mL, 1.0 mg/mL to 2.8 mg/mL, 1.2 mg/mL to 3.0 mg/mL, 1.2 mg/mL to 2.8 mg/mL, 0.6 mg/mL to 2.3 mg/mL, 0.6 mg/mL to 2.0 mg/mL, 0.6 mg/mL to 1.8 mg/mL, 0.6 mg/mL to 1.5 mg/mL, or 1.3 mg/mL to 2.8 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[1148]** 157. The method or the use of embodiment 155, wherein the GLP-1 receptor agonist is semaglutide and is present in the first pharmaceutical composition in an amount of 0.5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg.

**[1149]** 158. The method or the use of embodiment 155, wherein the GLP-1 receptor agonist is exenatide, and is present in the first pharmaceutical composition in a concentration of 5 µg/mL to 1000 µg/mL, 10 µg/mL to 900 µg/mL, 20 µg/mL to 800 µg/mL, 50 µg/mL to 700 µg/mL, 70 µg/mL to 600 µg/mL, 90 µg/mL to 550 µg/mL, 100 µg/mL to 500 µg/mL, 110 µg/mL to 450 µg/mL, 120 µg/mL to 400 µg/mL, 130 µg/mL to 350 µg/mL, 140

µg/mL to 350 µg/mL, 150 µg/mL to 300 µg/mL, 200 µg/mL to 300 µg/mL, or 200 µg/mL to 250 µg/mL, relative to a total volume of the first pharmaceutical composition.

**[1150]** 159. The method or the use of embodiment 155, wherein the GLP-1 receptor agonist is exenatide, and is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 5.0 mg/mL, 0.25 mg/mL to 4.5 mg/mL, 0.5 mg/mL to 4.5 mg/mL, 0.75 mg/mL to 4.0 mg/mL, 1.0 mg/mL to 3.75 mg/mL, 1.25 mg/mL to 3.5 mg/mL, 1.5 mg/mL to 3.25 mg/mL, 1.75 mg/mL to 3.0 mg/mL, 2.0 mg/mL to 2.75 mg/mL, or 2.25 mg/mL to 2.5 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[1151]** 160. The method or the use of embodiment 155, wherein the GLP-1 receptor agonist is dulaglutide and is present in the first pharmaceutical composition in a concentration 0.01 mg/mL to 100 mg/mL, 0.05 mg/mL to 90 mg/mL, 0.1 mg/mL to 80 mg/mL, 0.2 mg/mL to 70 mg/mL, 0.3 mg/mL to 60 mg/mL, 0.5 mg/mL to 50 mg/mL, 0.6 mg/mL to 45 mg/mL, 0.7 mg/mL to 40 mg/mL, 0.8 mg/mL to 35 mg/mL, 0.9 mg/mL to 30 mg/mL, 1.0 mg/mL to 25 mg/mL, 1.1 mg/mL to 20 mg/mL, 1.2 mg/mL to 15 mg/mL, or 1.5 mg/mL to 10 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[1152]** 161. The method or the use of embodiment 155, wherein the GLP-1 receptor agonist is orforglipron and is present in the first pharmaceutical composition in an amount of 0.01 mg to 100 mg, 0.05 mg to 90 mg, 0.1 mg to 80 mg, 0.2 mg to 70 mg, 0.3 mg to 60 mg, 0.4 mg to 50 mg, 0.5 mg to 45 mg, 0.6 mg to 40 mg, 0.7 mg to 35 mg, 0.8 mg to 30 mg, 0.9 mg to 25 mg, 1.0 mg to 20 mg, 1.1 mg to 18 mg, 1.2 mg to 16 mg, 1.3 mg to 14 mg, 1.4 mg to 12 mg, or 1.5 mg to 10 mg.

**[1153]** 162. The method or the use of any one of embodiments 152-154, wherein the GLP-1 receptor is a dual GLP-1/GIP receptor agonist and is present in the first pharmaceutical composition in a concentration of 5 mg/mL to 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[1154]** 163. The method or the use of embodiment 162, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and is present in the first pharmaceutical composition in a concentration of 5 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, or 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

**[1155]** 164. The method or the use of any one of embodiments 1 to 154, wherein the GLP-1 receptor agonist is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

**[1156]** 165. The method or the use of any one of embodiments 152 to 155, wherein the first pharmaceutical composition comprising the GLP-1 receptor agonist is administered to the subject parenterally.

**[1157]** 166. The method or the use of any one of embodiments 152 to 156, wherein the first pharmaceutical composition comprising the GLP-1 receptor agonist is administered to a subject subcutaneously.

**[1158]** 167. The method or the use of any one of embodiments 1 to 157, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's body weight is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[1159]** 168. The method or the use of any one of embodiments 1 to 158, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's fat mass is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

**[1160]** 169. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising:

administering a GLP-1 receptor agonist to the subject for at least one treatment cycle, wherein the subject failed to lose sufficient body weight and/or fat mass following administration of the GLP-1 receptor agonist for the at least one treatment cycle; and

administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295 to the subject after administration of the GLP-1 receptor agonist, such that the subject loses a sufficient amount of body weight and/or fat mass following administration of the non-naturally occurring melanocortin analog.

**[1161]** 170. Use of a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295 for reducing body weight and/or fat mass in a subject in need thereof who has failed to lose sufficient body weight and/or fat mass following administration of a GLP-1 receptor agonist for at least one treatment cycle, wherein the non-naturally occurring melanocortin analog is administered after administration of the GLP-1 receptor agonist such that the subject loses a sufficient amount of body weight and/or fat mass.

**[1162]** 171. A method of promoting weight loss in a subject currently being administered a GLP-1 receptor agonist, the method comprising administering to the subject a non-naturally occurring melanocortin analog, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[1163]** 172. Use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for reducing body weight and/or fat mass in a subject in need thereof, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[1164]** 173. The method or the use of embodiment 171 or 172, wherein the method or the use further comprises treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in the subject.

**[1165]** 174. The method or the use of any one of embodiments 171-173, wherein a plasma insulin level of the subject following administration of the non-naturally occurring melanocortin analog is substantially the same as a plasma insulin level of the subject prior to administration of the non-naturally occurring melanocortin analog.

**[1166]** 175. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising:

**[1167]** administering a combination therapy comprising:

(a) GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295,



wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[1168]** 176. Use of a combination therapy comprising:

(a) a GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295,

for reducing body weight and/or fat mass in a subject in need thereof, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

**[1169]** 177. The method or the use of any one of embodiments 1-175, wherein a blood glucose level of the subject is decreased following administration of a first dose of the combination therapy.

**[1170]** 178. The method or the use of any one of embodiments 1-177, wherein the GLP-1 receptor agonist is semaglutide and the combination therapy has an additive effect on the subject's weight loss.

**[1171]** 179. The method or the use of embodiment 178, wherein the combination therapy has an additive effect on the subject's fat mass loss.

**[1172]** 180. The method or the use of claim 282 or 283, wherein a percent lean mass of the subject is increased following administration of a first dose of the combination therapy.

**[1173]** 181. The method or the use of embodiment 178, wherein the combination therapy has an additive effect on suppressing the subject's appetite

**[1174]** 182. The method or the use of any one of embodiments 1-181, wherein the GLP-1 receptor agonist is a dual GLP-1/GIP receptor agonist.

**[1175]** 183. The method or the use of embodiment 182, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and the combination therapy has a synergistic effect on the subject's weight loss.

**[1176]** 184. The method or the use of embodiment 183, wherein the combination therapy has a synergistic effect on the subject's fat mass loss.

**[1177]** 185. The method or the use of embodiment 183, wherein the combination therapy has a synergistic effect on the suppressing the subject's appetite.

**[1178]** 186. The method or the use of any one of embodiments 1-185, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in body weight about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[1179]** 187. The method or the use of any one of embodiments 1-185, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, or about a 30% reduction in fat mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[1180]** 188. The method or the use of any one of embodiments 1-185, wherein the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[1181]** 189. The method or the use of any one of embodiments 1-185, wherein the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% increase in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[1182]** 190. The method or the use of any one of embodiments 1-185, wherein the subject exhibits about a 5%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, about a 30%, about a 35%, about a 40%, about a 45%, about a

50%, about a 60%, or about a 70% reduction, in food intake per day about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

**[1183]** 191. The method or the use of any one of embodiments 1-185, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in blood glucose level about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

## CLAIMS

I/We claim:

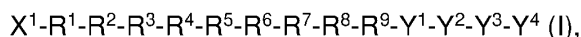
1. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising administering to the subject:

- (a) a GLP-1 receptor agonist; and
- (b) a non-naturally occurring melanocortin analog, to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject.

2. Use of (a) a non-naturally occurring melanocortin analog and (b) a GLP-1 receptor agonist for reducing body weight and/or fat mass in a subject in need thereof to produce an additive or synergistic effect on body weight and/or fat mass loss in the subject.

3. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising administering to the subject:

a non-naturally occurring melanocortin analog comprising a sequence of Formula (I):



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidinyl-proline (*cis*Pro(guan)), and *trans*-4-guanidinyl-proline (*trans*Pro(guan));

R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;

R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

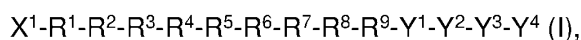
provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys a R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

4. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I):



wherein:

$X^1$  is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

$R^1$  is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

$R^2$  is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

$R^3$  is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

$R^4$  is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

$R^5$  is selected from the group consisting of His, Arg, *cis*-4-guanidinyI-proline (*cis*Pro(guan)), and *trans*-4-guanidinyI-proline (*trans*Pro(guan));

$R^6$  is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

$R^7$  is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

$R^8$  is absent, Lys, or Trp;

$R^9$  is absent or Lys;

$Y^1$  is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

$Y^2$  is selected from the group consisting of dVal, dPro, and dTle;

$Y^3$  is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

5. The method or the use of any one of claims 1-4, wherein the method further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

6. The method or the use of claim 5, wherein the lean mass is lean muscle mass.

7. The method or the use of any one of claims 1 to 6, wherein the method further comprises treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in the subject.

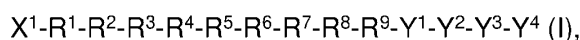
8. A method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising administering to the subject:

- (a) a GLP-1 receptor agonist; and
- (b) a non-naturally occurring melanocortin analog, to produce a synergistic or additive effect on glucose intolerance and/or diabetes mellitus in the subject.

9. Use of (a) a non-naturally occurring melanocortin analog and (b) a GLP-1 receptor agonist for treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof to produce a synergistic or additive effect on glucose intolerance and/or diabetes mellitus in the subject

10. A method of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising administering to the subject:

a non-naturally occurring melanocortin analog comprising a sequence of Formula:



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));



R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;

R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

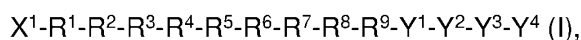
provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

11. Use of a non-naturally occurring melanocortin analog for treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in a subject in need thereof, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I):



wherein:

$X^1$  is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

$R^1$  is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

$R^2$  is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

$R^3$  is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

$R^4$  is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

$R^5$  is selected from the group consisting of His, Arg, *cis*-4-guanidinyI-proline (*cis*Pro(guan)), and *trans*-4-guanidinyI-proline (*trans*Pro(guan));

$R^6$  is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

$R^7$  is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

$R^8$  is absent, Lys, or Trp;

$R^9$  is absent or Lys;

$Y^1$  is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

$Y^2$  is selected from the group consisting of dVal, dPro, and dTle;

$Y^3$  is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

12. The method or the use of any one of claims 8-11, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

13. The method or the use of claim 12, wherein the lean mass is lean muscle mass.

14. The method or the use of any one of claims 8 to 13, wherein the method or the use further comprises reducing body weight and/or fat mass in the subject.

15. The method or the use of any one of claims 8 to 14, wherein the method or the use further comprises treating, preventing, reducing, or otherwise ameliorating a sleep disorder in the subject.

16. The method or the use of claim 15, wherein the sleep disorder is sleep apnea.

17. The method or the use of any one of claims 1 to 14, wherein the GLP-1 receptor agonist is administered at a dose that is less than a dose required to elicit a response in the subject without the non-naturally occurring melanocortin analog.

18. The method or the use of any one of claims 1 to 15, wherein the non-naturally occurring melanocortin analog is administered at a dose that is less than a dose required to elicit a response in the subject without the GLP-1 receptor agonist or a dual GLP-1/GIP receptor agonist.

19. The method or the use of any one of claims 1 to 16, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 0.01 mg to about 10 mg once per week.

20. The method or the use of claim 19, wherein semaglutide is administered subcutaneously at a dose of less than 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2 mg, or 2.4 mg once per week.

21. The method or the use of any one of claims 1 to 16, wherein the GLP-1 receptor agonist is semaglutide and is administered at a dose of about 0.5 mg to about 40 mg once daily.

22. The method or the use of claim 21, wherein semaglutide is administered orally at a dose of less than 3 mg, 7 mg or 14 mg once daily.

23. The method or the use of any one of claims 1 to 16, wherein the GLP-1

receptor agonist is semaglutide and is administered at a dose of about 12.5 nmol/kg or 25 nmol/kg per body weight of the subject once every three days.

24. The method or the use of any one of claims 1 to 16, wherein the GLP-1 receptor agonist is exenatide and is administered at a dose of about 0.5 µg to about 100 µg twice daily.

25. The method or the use of claim 24, wherein exenatide is administered subcutaneously at a dose of less than 5 µg or 10 µg twice daily.

26. The method or the use of any one of claims 1 to 16, wherein the GLP-1 receptor agonist is exenatide and is administered at a dose of about 0.5 mg to about 50 mg once per week.

27. The method or the use of claim 26, wherein exenatide is administered subcutaneously at a dose of less than 2 mg once per week.

28. The method or the use of any one of claims 1 to 16, wherein the GLP-1 receptor agonist is dulaglutide and is administered at a dose of about 0.05 mg to about 50 mg once per week.

29. The method or the use of claim 28, wherein dulaglutide is administered subcutaneously at a dose of less than 0.75 mg, 1.5 mg, 3.0 mg or 4.5 mg once per week.

30. The method or the use of any one of claims 1 to 16, wherein the GLP-1 receptor agonist is orforglipron and is administered at a dose of about 0.01 mg to about 100 mg once daily.

31. The method or the use of claim 30, wherein orforglipron is administered orally at a dose of less than 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, or 24 mg once daily.

32. The method or the use of any one of claims 1 to 16, wherein the GLP-1 receptor agonist is a dual GLP-1/GIP receptor agonist.

33. The method or the use of claim 32, wherein the dual GIP/GLP-1 receptor agonist is tirzepatide and is administered at a dose of about 0.5 mg to about 50 mg once per week.

34. The method or the use of claim 33, wherein tirzepatide is administered subcutaneously at a dose of less than 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg once per week.

35. The method or the use of claim 32, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and is administered at a dose of about 12.5 nmol/kg or 25 nmol/kg per body weight of the subject once every three days.

36. The method or the use of any one of claims 1 to 33, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.5 mg/kg to about 10 mg/kg per body weight of the subject once daily.

37. The method or the use of claim 36, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 1 mg/kg or 3 mg/kg per body weight of the subject once daily.

38. The method or the use of any one of claims 1 to 33, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

39. The method or the use of any one of claims 1 to 33, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

40. The method or the use of any one of claims 1 to 37, wherein the melanocortin 4 receptor agonist is an agonist of the melanocortin 3 receptor.

41. The method or the use of claim 40, wherein the melanocortin 4 receptor agonist is a full agonist of the melanocortin 3 receptor.

42. The method or the use of claim 40 or 41, wherein the non-naturally occurring melanocortin agonist comprises no melanocortin 3 receptor antagonist activity.

43. The method or the use of any one of claims 1 to 42, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to administration of the GLP-1 receptor agonist, and wherein administration of the non-naturally occurring melanocortin analog makes the subject more responsive to the GLP-1 receptor agonist, compared to a subject who has not been administered the non-naturally occurring melanocortin 4 receptor analog.

44. The method or the use of any one of claims 1 to 42, wherein the non-naturally occurring melanocortin agonist is administered to the subject after administration of the GLP-1 receptor agonist, and wherein the subject failed to lose sufficient body weight and/or fat mass following administration with the GLP-1 receptor agonist without the non-naturally occurring melanocortin analog.

45. The method or the use of claim 44, wherein the non-naturally occurring melanocortin analog is administered to the subject after administration of the GLP-1 receptor agonist for one dose, one week, or one cycle.

46. The method or the use of claim 44, wherein the non-naturally occurring melanocortin analog is administered to the subject after treatment with the GLP-1 receptor agonist is complete.

47. The method or the use of any one of claims 1 to 42, wherein the GLP-1 receptor agonist is administered to the subject for a period of time before administration of the non-naturally occurring melanocortin analog, and wherein, while the non-naturally occurring melanocortin analog is administered to the subject, administration of the GLP-1 receptor agonist is paused, and wherein, when administration of the non-naturally occurring melanocortin analog is completed, administration of the GLP-1 receptor agonist is resumed.

48. The method or the use of any one of claims 1 to 42, wherein the non-naturally occurring melanocortin analog is administered to the subject for a period of time before administration of the GLP-1 receptor agonist, and wherein, while a non-GLP-1 receptor agonist is administered to the subject, administration of the non-naturally occurring melanocortin analog is paused, and wherein, when administration of the GLP-1 receptor agonist is completed, administration of the non-naturally occurring melanocortin analog is resumed.

49. The method or the use of any one of claims 1 to 46, wherein the method or the use further comprises preventing or reducing one or more side effects associated with the GLP-1 receptor agonist.

50. The method or the use of claim 49, wherein the one or more side effects associated with the GLP-1 receptor agonist is a gastrointestinal effect.

51. The method or the use of claim 50, wherein the gastrointestinal effect is one or more of nausea, vomiting, and diarrhea.

52. The method or the use of any one of claims 49 to 51, wherein the one or more side effects associated with the GLP-1 receptor agonist is an adverse cardiovascular event.

53. The method or the use of claim 52, wherein the adverse cardiovascular event is one or more of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous



coronary intervention, heart failure, carotid endarterectomy, and peripheral vascular disease.

54. The method or the use of any one of claims 1 to 51, wherein the method or the use further comprises preventing or reducing one or more side effects associated with the non-naturally occurring melanocortin analog.

55. The method or the use of any one of claims 54, wherein the one or more side effects associated with the non-naturally occurring melanocortin analog is an adverse cardiovascular event.

56. The method or the use of claim 55, wherein the adverse cardiovascular event is sinus tachycardia.

57. The method or the use of any one of claims 1 to 54, wherein the method or the use further comprises reducing obesity-related inflammation in the subject.

58. The method or the use of any one of claims 1 to 55, wherein the method or the use further comprises preserving or improving kidney function in the subject.

59. A method of treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with the use of a GLP-1 receptor agonist in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the GLP-1 receptor agonist.

60. Use of a non-naturally occurring melanocortin analog for treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with the use of a GLP-1 receptor agonist in a subject, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to, during, and/or after administration of the GLP-1 receptor agonist.

61. The method or the use of claim 59 or 60, wherein the GLP-1 receptor is administered at a dose sufficient to elicit weight loss in the subject, and wherein the dose sufficient to elicit weight loss in the subject is lower than a dose of the GLP-1 receptor agonist required to elicit weight loss in the subject without the non-naturally occurring melanocortin analog.

62. The method or the use of any one of claims 59-61, wherein the one or more side effects associated with the use of a GLP-1 receptor agonist is an adverse cardiovascular event.

63. The method or the use of claim 62, wherein the adverse cardiovascular event is one or more of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, and peripheral vascular disease.

64. The method or the use of any one of claims 59-61, wherein the one or more side effects associated with the use of the GLP-1 receptor agonist is a gastrointestinal effect.

65. The method or the use of claim 64, wherein the gastrointestinal effect is one or more of nausea, vomiting, and diarrhea.

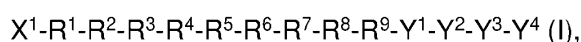
66. A method of reducing obesity-related inflammation in a subject in need thereof, comprising administering to the subject:

- (a) a GLP-1 receptor agonist; and
- (b) a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist

67. Use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for reducing obesity-related inflammation in a subject in need thereof, wherein the

non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

68. A method of reducing obesity-related inflammation in a subject in need thereof, comprising administering to the subject a non-naturally occurring melanocortin analog comprising a sequence of Formula (I):



wherein:

$X^1$  is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

$R^1$  is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

$R^2$  is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

$R^3$  is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

$R^4$  is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

$R^5$  is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

$R^6$  is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

$R^7$  is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

$R^8$  is absent, Lys, or Trp;

$R^9$  is absent or Lys;

$Y^1$  is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

$Y^2$  is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

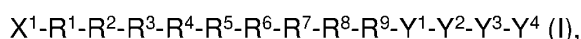
provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

69. Use of a non-naturally occurring melanocortin analog for reducing obesity-related inflammation in a subject in need thereof, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I):



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;

R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

70. A method of preserving or improving kidney function in a subject in need thereof, comprising administering to the subject:

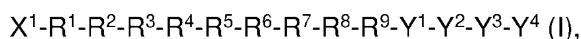
(a) a GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

71. Use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for preserving or improving kidney function in a subject in need thereof, wherein the non-naturally occurring melanocortin analog is administered prior to, during, or after administration of the GLP-1 receptor agonist.

72. A method of preserving or improving kidney function in a subject in need thereof, comprising administering to the subject:

a non-naturally occurring melanocortin analog comprising a sequence of Formula (I):



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;

R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

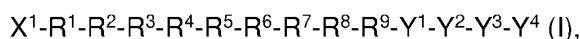
provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

73. Use of a non-naturally occurring melanocortin analog for preserving or improving kidney function in a subject in need thereof, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I):



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;



R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

74. The method or the use of any one of claims 1 to 73, wherein the subject has a metabolic dysfunction selected from the group consisting of obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies.

75. The method or the use of any one of claims 1-74, wherein the method or the use increases tolerance for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

76. The method or the use of claim 75, wherein the increased tolerance comprises reduced nausea.

77. The method or the use of any one of claims 1-76, wherein the method or the use maintains or increases a muscle mass level relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

78. The method or the use of claim 77, wherein the muscle mass comprises lean muscle mass.

79. The method or the use of any one of claims 1-78, wherein the method or the use increases a preference level or a compliance level for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

80. The method or the use of any one of claims 1-79, wherein the method or the use comprises increasing a weight loss level for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

81. The method or the use of any one of claims 1-80, wherein the method or the use comprises a reduction in one or more side effects associated with the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

82. The method or the use of any one of claims 1-81, wherein the method or the use comprises reducing a weight loss plateau for the GLP-1 receptor agonist relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

83. The method or the use of any one of claims 1-82, wherein the method or the use reduces an appetite level or a weight gain level relative to a treatment comprising administration of a GLP-1 receptor agonist without a non-naturally occurring melanocortin analog.

84. The method or the use of any one of claims 1-83, wherein the method or the use does not reduce efficacy of the GLP-1 receptor agonist relative to a control.

85. The method or the use of any one of claims 1-83, wherein the method or the use increases efficacy of the GLP-1 receptor agonist relative to a control.

86. The method or the use of any one of claims 1-83, wherein the method or the use does not plateau body weight loss in the subject.

87. The method or the use of any one of claims 1-83, wherein the method or the use does not plateau fat mass loss in the subject.

88. The method or the use of any one of claims 1-87, wherein the method or the use prevents fat mass gain after administration of the GLP-1 receptor agonist relative to a control.

89. The method or the use of any one of claims 1-88, wherein the method or the use prevents body weight gain after administration of the GLP-1 receptor agonist relative to a control.

90. The method or the use of any one of claims 1-88, wherein the method or the use reduces body weight gain after administration of the GLP-1 receptor agonist relative to a control.

91. The method or the use of any one of claims 1-88, wherein the method or the use reduces fat mass gain after administration of the GLP-1 receptor agonist relative to a control.

92. The method or the use of any one of claims 1-91, wherein the method or the use reduces a blood sugar level in the subject relative to a control.

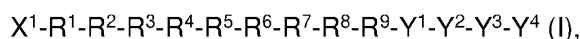
93. The method or the use of any one of claims 1-91, wherein the method or the use prevents a blood sugar elevation in the subject after administration of the GLP-1 receptor agonist relative to a control.

94. The method or the use of any one of claims 1-91, wherein the method or the use reduces a blood sugar elevation in the subject after administration of the GLP-1 receptor agonist relative to a control.

95. The method or the use of any one of claims 1-94, wherein the method or the use maintains or increases brain mass in the subject during or after administration of the GLP-1 receptor agonist relative to a control.

96. The method or the use of any one of claims 1-94, wherein the method or the use prevents or reduces brain mass loss in the subject during or after administration of the GLP-1 receptor agonist relative to a control.

97. The method or the use of any one of claims 1-96, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I):



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;

R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

provided that:

when one or both of R<sup>2</sup> and R<sup>3</sup> is Phe, then the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R<sup>1</sup> and Lys at R<sup>9</sup>;

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present and Y<sup>4</sup> is absent, or (ii) X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are absent, R<sup>1</sup> is Nle, R<sup>4</sup> is dPhe, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated; and

when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

98. The method or the use of any one of claims 1-96, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I), wherein: X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), proline (Pro), Ala, D-alanine (dAla), and phenylalanine (Phe);

R<sup>3</sup> is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R<sup>4</sup> is selected from the group consisting of Pro, D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is selected from the group consisting of Arg, Pro, cysteine (Cys) and lysine (Lys);

R<sup>8</sup> is absent, Lys, or Trp;

R<sup>9</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys;

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> or R<sup>8</sup> is Lys; and

a lactam bridge between R<sup>1</sup> and R<sup>9</sup> when R<sup>1</sup> is Asp, R<sup>6</sup> is dPhe, and R<sup>9</sup> is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

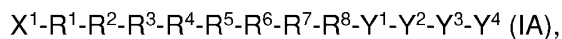
Ac-Nle-c[Asp-Phe-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 366);  
Ac-Nle-c[Asp-Phe-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 412);  
Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 423);  
Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 424);  
Ac-Nle-c[Asp-Phe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 487);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218);  
Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 225);  
Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231);  
Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302);  
His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 306);  
dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 309);  
Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 311);  
Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 312);  
Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 313);  
Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 314);  
Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 315);  
Ac-Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 413);  
Ac-Nle-c[Asp-dHis-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 416);  
Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 425);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435);



Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436);  
Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 437);  
Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 438);  
Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 439);  
Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 440);  
Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 441);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 443);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 447);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453);  
Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 454);  
Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 455);  
Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 456);  
Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 457);  
Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 458);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617);  
 Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620);  
 Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628);  
 Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591);  
 Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592);  
 Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593);  
 Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594);  
 Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 597);  
 Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 598);  
 Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638);  
 Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640);  
 Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641);  
 Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 642);  
 Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 643);  
 Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 644);  
 Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 645);  
 Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 646);  
 Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); and  
 Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

99. The method or the use of any one of claims 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IA):



wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, Ala, and D-alanine (dAla);

R<sup>3</sup> is His or dHis;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is His or Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Pro or lysine (Lys);

R<sup>8</sup> is absent or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is dVal or dPro;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp and R<sup>7</sup> or R<sup>8</sup> is Lys;

provided that when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

100. The method or the use of any one of claims 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IA), wherein:

X<sup>1</sup> is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, aspartic acid (Asp), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is selected from the group consisting of Asp, Ala, and D-alanine (dAla);

R<sup>3</sup> is His or dHis;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is His or Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Pro or lysine (Lys);

R<sup>8</sup> is absent or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is dVal or dPro;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

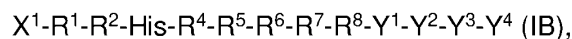
the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp and R<sup>7</sup> or R<sup>8</sup> is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise the sequence:

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

101. The method or the use of any one of claims 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IB):



wherein:

X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, dArg, alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is Asp;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is selected from the group consisting of His, Arg, *cis*-4-guanidiny-proline (*cis*Pro(guan)), and *trans*-4-guanidiny-proline (*trans*Pro(guan));

R<sup>6</sup> is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is Pro or Lys;

R<sup>8</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>2</sup> is Asp, and R<sup>7</sup> or R<sup>8</sup> is Lys.

102. The method or the use of claim 101, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IB), wherein:

X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, Arg, lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R<sup>2</sup> is Asp;

R<sup>4</sup> is D-phenylalanine (dPhe) or para-fluoro-D-phenylalanine (p(F)dPhe);

R<sup>5</sup> is His or Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Pro or Lys;

R<sup>8</sup> is absent or Lys;

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

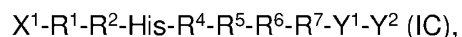
Y<sup>2</sup> is dVal or dPro;

Y<sup>3</sup> is absent, dVal, or dPro;

Y<sup>4</sup> is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R<sup>2</sup> and R<sup>7</sup> or R<sup>8</sup> when R<sup>2</sup> is Asp, and R<sup>7</sup> or R<sup>8</sup> is Lys.

103. The method or the use of any one of claims 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IC):



wherein:

X<sup>1</sup> is norleucine (Nle), arginine (Arg) or D-arginine (dArg);

R<sup>1</sup> is aspartic acid (Asp);

R<sup>2</sup> is alanine (Ala) or D-alanine (dAla);

R<sup>4</sup> is D-phenylalanine (dPhe);

R<sup>5</sup> is Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Lys;

Y<sup>1</sup> is D-valine (dVal);

Y<sup>2</sup> is D-proline (dPro); and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R<sup>2</sup> and Lys at R<sup>7</sup>;

provided that when R<sup>2</sup> is Ala, then X<sup>1</sup> is Nle.

104. The method or the use of any one of claims 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IC), wherein:

X<sup>1</sup> is norleucine (Nle), arginine (Arg) or D-arginine (dArg);

R<sup>1</sup> is aspartic acid (Asp);

R<sup>2</sup> is alanine (Ala) or D-alanine (dAla);

R<sup>4</sup> is D-phenylalanine (dPhe);

R<sup>5</sup> is Arg;

R<sup>6</sup> is tryptophan (Trp);

R<sup>7</sup> is Lys;

Y<sup>1</sup> is D-valine (dVal);

Y<sup>2</sup> is D-proline (dPro); and

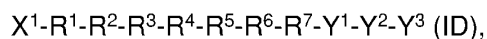
the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R<sup>2</sup> and Lys at R<sup>7</sup>;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence of:

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 381); or

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 382).

105. The method or the use of any one of claims 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (ID):



wherein:

X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro);

R<sup>3</sup> is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro);

R<sup>4</sup> is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of Arg, *cis*-4-guanidinyI-proline (*cis*Pro(guan)), and *trans*-4-guanidinyI-proline (*trans*Pro(guan));

R<sup>6</sup> is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is cysteine (Cys) or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys; and

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> is Lys;

provided that:

when R<sup>3</sup> is Pro, then R<sup>4</sup> is dPhe and either (i) X<sup>1</sup> and Y<sup>3</sup> are present, or (ii) X<sup>1</sup> and Y<sup>3</sup> are absent, R<sup>1</sup> is Nle, R<sup>5</sup> is Arg, R<sup>6</sup> is Trp, Y<sup>1</sup>Y<sup>2</sup> is dVal-dPro, and the C-terminus is amidated;

when R<sup>4</sup> is dPhe, then (i) R<sup>3</sup> is not His or Gln or (ii) R<sup>3</sup> is His and either R<sup>2</sup> is Pro or R<sup>5</sup> is *trans*Pro(guan) or *cis*Pro(guan); and

when R<sup>4</sup> is p(F)dPhe, R<sup>3</sup> is His, and R<sup>1</sup> is Nle, then (i) R<sup>6</sup> is not Trp or (ii) Y<sup>3</sup> is dVal.

106. The method or the use of any one of claims 1-98, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (ID), wherein:



X<sup>1</sup> is absent or is norleucine (Nle);

R<sup>1</sup> is selected from the group consisting of Nle, D-arginine (dArg), aspartic acid (Asp), and alanine (Ala);

R<sup>2</sup> is selected from the group consisting of Asp, D-cysteine (dCys), and proline (Pro);

R<sup>3</sup> is selected from the group consisting of histidine (His), glutamine (Gln), and proline (Pro);

R<sup>4</sup> is selected from the group consisting of D-phenylalanine (dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R<sup>5</sup> is selected from the group consisting of Arg, *cis*-4-guanidinyI-proline (*cis*Pro(guan)), and *trans*-4-guanidinyI-proline (*trans*Pro(guan));

R<sup>6</sup> is tryptophan (Trp) or 2'-D-naphthylalanine (dNal(2'));

R<sup>7</sup> is cysteine (Cys) or lysine (Lys);

Y<sup>1</sup> is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y<sup>2</sup> is selected from the group consisting of dVal, dPro, and dTle;

Y<sup>3</sup> is absent, dVal, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R<sup>2</sup> and R<sup>7</sup> when R<sup>2</sup> is dCys, R<sup>4</sup> is p(Cl)dPhe, and R<sup>7</sup> is Cys; and

a lactam bridge between R<sup>1</sup> or R<sup>2</sup> and R<sup>7</sup> when R<sup>1</sup> or R<sup>2</sup> is Asp, R<sup>4</sup> is dPhe or p(F)dPhe, and R<sup>7</sup> is Lys;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 218);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 225);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 231);  
Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 232);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 300);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 302);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 430);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 435);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 436);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 442);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 444);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 446);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 448);  
Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 449);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 450);  
Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 451);  
Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 452);  
Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 453);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 595);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 596);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 617);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 620);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 628);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 591);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 592);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 593);  
Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH<sub>2</sub> (SEQ ID NO: 594);  
Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 638);  
Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 640);  
Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 641);  
Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363);  
Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370);  
Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621);  
Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223);  
Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469);  
Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475);  
Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and  
Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478).

107. The method or the use of any one of claims 3-106, wherein an N-terminus of the non-naturally occurring melanocortin analog, if present, is modified by an acyl group.

108. The method or the use of claim 107, wherein the acyl group is an acetyl group.

109. The method or the use of any one of claims 3-106, wherein an N-terminus of the non-naturally occurring melanocortin analog, if present, is not modified.

110. The method or the use of any one of claims 3-109, wherein a C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group.

111. The method or the use of any one of claims 3-109, wherein a C-terminus of the non-naturally occurring melanocortin analog is not modified.

112. The method or the use of any one of claims 3-111, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond.

113. The method or the use of any one of claims 3-112, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between  $R^2$  and  $R^7$ .

114. The method or the use of any one of claims 3-113, wherein  $R^4$  is dPhe or p(F)dPhe.

115. The method or the use of any one of claims 3-114, wherein  $R^3$  is His.

116. The method or the use of any one of claims 3-115, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 223);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 476);

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 363); and

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH<sub>2</sub> (SEQ ID NO: 621),

wherein c represents cyclization through  $R^2$  and  $R^7$  via a lactam bond.

117. The method or the use of any one of claims 3-115, wherein  $R^4$  is p(F)dPhe.

118. The method or the use of claim 117, wherein  $R^1$  is selected from the group consisting of Ala, Arg, dArg, Lys, dLys, His, and dHis.

119. The method or the use of claim 117 or 118, wherein  $Y^1$  is dVal and  $Y^2$  is dPro.

120. The method or the use of any one of claims 3-115 and 117-119, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 462);

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 463);  
Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 464);  
Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 465);  
Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 466);  
Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 467); and  
Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 468),  
wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

121. The method or the use of claim 117 or 118, wherein Y<sup>1</sup> is dTle and Y<sup>2</sup> is dPro.

122. The method or the use of any one of claims 3-115, 117, 118, and 121, wherein the sequence according of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 479);  
Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 480);  
Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 481);  
Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 482);  
Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 483);  
Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 484); and  
Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 485),  
wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

123. The method or the use of any one of claims 3-115, wherein R<sup>4</sup> is p(F)dPhe.

124. The method or the use of claim 123, wherein at least one of X<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> is present.

125. The method or the use of any one of claims 3-115, 124, and 123, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 469);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH<sub>2</sub> (SEQ ID NO: 473);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 474);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 475);

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH<sub>2</sub> (SEQ ID NO: 477); and

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 478),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

126. The method or the use of any one of claims 3-115, wherein R<sup>5</sup> is selected from the group consisting of His, *trans*Pro(guan) and *cis*Pro(gaun).

127. The method or the use of any one of claims 3-115 and 126, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-His-dPhe-*trans*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 228);

Ac-Nle-c[Asp-His-dPhe-*cis*Pro(guan)-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 229); and

Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 470),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

128. The method or the use of any one of claims 3-115, wherein R<sup>6</sup> is dNal(2').

129. The method or the use of any one of claims 3-115 and 128, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 471), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

130. The method or the use of any one of claims 3-114, wherein R<sup>3</sup> is not His.

131. The method or the use of any one of claims 3-114 and 130, wherein R<sup>3</sup> is selected from the group consisting of dHis, Gln, and Pro.

132. The method or the use of any one of claims 3-115, 130, and 131, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 365);

Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 370);

Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 486);

Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 491); and

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 639),

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

133. The method or the use of any one of claims 3-112, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R<sup>1</sup> and R<sup>7</sup> or R<sup>2</sup> and R<sup>8</sup>.

134. The method or the use of any one of claims 3-112 and 133, wherein R<sup>4</sup> is dPhe.

135. The method or the use of any one of claims 3-112, 133, and 134, wherein R<sup>3</sup> is His.

136. The method or the use of any one of claims 3-112 and 133-135, wherein X<sup>1</sup> and R<sup>1</sup> are present.

137. The method or the use of any one of claims 3-112 and 133-136, wherein R<sup>2</sup> is Ala or dAla.

138. The method or the use of any one of claims 3-112 and 133-137, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 268);

Ac-Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 378);

Ac-dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 379); and

Ac-Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 380),

wherein c represents cyclization through R<sup>1</sup> and R<sup>7</sup> via a lactam bond.

139. The method or the use of any one of claims 3-112 and 133-135, wherein either R<sup>2</sup> of R<sup>7</sup> is Pro.

140. The method or the use of any one of claims 3-112, 133-135, and 139, wherein the sequence of any one of Formulae (I)-(ID) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 297); or

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 418).

wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a lactam bond.

141. The method or the use of any one of claims 3-112, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a lactam bond between R<sup>1</sup> and R<sup>9</sup>.

142. The method or the use of any one of claims 3-112 and 141, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 420), wherein c represents cyclization through R<sup>1</sup> and R<sup>9</sup> via a lactam bond.

143. The method or the use of any one of claims 3-111, wherein the sequence of any one of Formulae (I)-(ID) is cyclized by a disulfide bond.



144. The method or the use of any one of claims 3-111 and 142, wherein R<sup>4</sup> is p(Cl)dPhe.

145. The method or the use of any one of claims 3-111, 142, and 143, wherein the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro-NH<sub>2</sub> (SEQ ID NO: 498), wherein c represents cyclization through R<sup>2</sup> and R<sup>7</sup> via a disulfide bond.

146. The method or the use of any one of claims 1-96, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 228, 229, 268, 295, 297, 363, 365, 370, 378-380, 418, 420, 462-471, 473-486, 491, and 498.

147. The method or the use of claim 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 268, 363, 365, 378-380, 418, 464-470, 474-478, and 481-486.

148. The method or the use of claim 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 228-229, 363, 418, 462-485, and 621.

149. The method or the use of claim 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 223, 363, 418, 464-470, 474-478, 481-485, and 621.

150. The method or the use of claim 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 268 and 378-380.

151. The method or the use of claim 143, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 228, 229, 295, 297, 462, 463, 471, 473, 479, 480, 491, and 498.

152. The method or the use of any one of claims 1-151, wherein the GLP-1 receptor agonist is present in a first pharmaceutical composition.

153. The method or the use of claim 152, wherein the first pharmaceutical composition comprises one or more pharmaceutically acceptable excipients and/or carriers.

154. The method or the use of claim 153, wherein the one or more pharmaceutically acceptable excipients and/or carriers of the first pharmaceutical composition comprise water.

155. The method or the use of any one of claims 152-154, wherein the GLP-1 receptor agonist is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition.

156. The method or the use of claim 155, wherein the GLP-1 receptor agonist is semaglutide and is present in the first pharmaceutical composition in a concentration of 0.5 mg/mL to 5.0 mg/mL, 0.5 mg/mL to 4.0 mg/mL, 0.6 mg/mL to 3.5 mg/mL, 0.65 mg/mL to 3.2 mg/mL, 0.65 mg/mL to 3.0 mg/mL, 0.8 mg/mL to 2.8 mg/mL, 1.0 mg/mL to 3.0 mg/mL, 1.0 mg/mL to 2.8 mg/mL, 1.2 mg/mL to 3.0 mg/mL, 1.2 mg/mL to 2.8 mg/mL, 0.6 mg/mL to 2.3 mg/mL, 0.6 mg/mL to 2.0 mg/mL, 0.6 mg/mL to 1.8 mg/mL, 0.6 mg/mL to 1.5 mg/mL, or 1.3 mg/mL to 2.8 mg/mL, relative to a total volume of the first pharmaceutical composition.

157. The method or the use of claim 155, wherein the GLP-1 receptor agonist is semaglutide and is present in the first pharmaceutical composition in an amount of 0.5 mg to 40 mg, 0.5 mg to 30 mg, 1 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 20 mg, 2 mg to 20 mg, 0.5 mg to 15 mg, 1 mg to 15 mg, 2 mg to 15 mg, 3 mg to 15 mg, 5 mg to 15 mg, 0.5 mg to 10 mg, 1 mg to 10 mg, or 5 mg to 10 mg.

158. The method or the use of claim 155, wherein the GLP-1 receptor agonist is

exenatide, and is present in the first pharmaceutical composition in a concentration of 5 µg/mL to 1000 µg/mL, 10 µg/mL to 900 µg/mL, 20 µg/mL to 800 µg/mL, 50 µg/mL to 700 µg/mL, 70 µg/mL to 600 µg/mL, 90 µg/mL to 550 µg/mL, 100 µg/mL to 500 µg/mL, 110 µg/mL to 450 µg/mL, 120 µg/mL to 400 µg/mL, 130 µg/mL to 350 µg/mL, 140 µg/mL to 350 µg/mL, 150 µg/mL to 300 µg/mL, 200 µg/mL to 300 µg/mL, or 200 µg/mL to 250 µg/mL, relative to a total volume of the first pharmaceutical composition.

159. The method or the use of claim 155, wherein the GLP-1 receptor agonist is exenatide, and is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 5.0 mg/mL, 0.25 mg/mL to 4.5 mg/mL, 0.5 mg/mL to 4.5 mg/mL, 0.75 mg/mL to 4.0 mg/mL, 1.0 mg/mL to 3.75 mg/mL, 1.25 mg/mL to 3.5 mg/mL, 1.5 mg/mL to 3.25 mg/mL, 1.75 mg/mL to 3.0 mg/mL, 2.0 mg/mL to 2.75 mg/mL, or 2.25 mg/mL to 2.5 mg/mL, relative to a total volume of the first pharmaceutical composition.

160. The method or the use of claim 155, wherein the GLP-1 receptor agonist is dulaglutide and is present in the first pharmaceutical composition in a concentration 0.01 mg/mL to 100 mg/mL, 0.05 mg/mL to 90 mg/mL, 0.1 mg/mL to 80 mg/mL, 0.2 mg/mL to 70 mg/mL, 0.3 mg/mL to 60 mg/mL, 0.5 mg/mL to 50 mg/mL, 0.6 mg/mL to 45 mg/mL, 0.7 mg/mL to 40 mg/mL, 0.8 mg/mL to 35 mg/mL, 0.9 mg/mL to 30 mg/mL, 1.0 mg/mL to 25 mg/mL, 1.1 mg/mL to 20 mg/mL, 1.2 mg/mL to 15 mg/mL, or 1.5 mg/mL to 10 mg/mL, relative to a total volume of the first pharmaceutical composition.

161. The method or the use of claim 155, wherein the GLP-1 receptor agonist is orforglipron and is present in the first pharmaceutical composition in an amount of 0.01 mg to 100 mg, 0.05 mg to 90 mg, 0.1 mg to 80 mg, 0.2 mg to 70 mg, 0.3 mg to 60 mg, 0.4 mg to 50 mg, 0.5 mg to 45 mg, 0.6 mg to 40 mg, 0.7 mg to 35 mg, 0.8 mg to 30 mg, 0.9 mg to 25 mg, 1.0 mg to 20 mg, 1.1 mg to 18 mg, 1.2 mg to 16 mg, 1.3 mg to 14 mg, 1.4 mg to 12 mg, or 1.5 mg to 10 mg.

162. The method or the use of any one of claims 152-154, wherein the GLP-1 receptor is a dual GLP-1/GIP receptor agonist and is present in the first pharmaceutical

composition in a concentration of 5 mg/mL to 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

163. The method or the use of claim 162, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and is present in the first pharmaceutical composition in a concentration of 5 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, or 30 mg/mL, relative to a total volume of the first pharmaceutical composition.

164. The method or the use of any one of claims 1 to 154, wherein the GLP-1 receptor agonist is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

165. The method or the use of any one of claims 152 to 155, wherein the first pharmaceutical composition comprising the GLP-1 receptor agonist is administered to the subject parenterally.

166. The method or the use of any one of claims 152 to 156, wherein the first pharmaceutical composition comprising the GLP-1 receptor agonist is administered to a subject subcutaneously.

167. The method or the use of any one of claims 1 to 157, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's body weight is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

168. The method or the use of any one of claims 1 to 158, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's fat mass is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

169. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising:

administering a GLP-1 receptor agonist to the subject for at least one treatment cycle, wherein the subject failed to lose sufficient body weight and/or fat mass following administration of the GLP-1 receptor agonist for the at least one treatment cycle; and

administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295 to the subject after administration of the GLP-1 receptor agonist, such that the subject loses a sufficient amount of body weight and/or fat mass following administration of the non-naturally occurring melanocortin analog.

170. Use of a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295 for reducing body weight and/or fat mass in a subject in need thereof who has failed to lose sufficient body weight and/or fat mass following administration of a GLP-1 receptor agonist for at least one treatment cycle, wherein the non-naturally occurring melanocortin analog is administered after administration of the GLP-1 receptor agonist such that the subject loses a sufficient amount of body weight and/or fat mass.

171. A method of promoting weight loss in a subject currently being administered a GLP-1 receptor agonist, the method comprising administering to the subject a non-naturally occurring melanocortin analog, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

172. Use of a non-naturally occurring melanocortin analog and a GLP-1 receptor agonist for reducing body weight and/or fat mass in a subject in need thereof, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

173. The method or the use of claim 171 or 172, wherein the method or the use further comprises treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in the subject.

174. The method or the use of any one of claims 171-173, wherein a plasma insulin level of the subject following administration of the non-naturally occurring melanocortin analog is substantially the same as a plasma insulin level of the subject prior to administration of the non-naturally occurring melanocortin analog.

175. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising:

administering a combination therapy comprising:

(a) GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295,

wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

176. Use of a combination therapy comprising:

(a) a GLP-1 receptor agonist; and

(b) a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 295,

for reducing body weight and/or fat mass in a subject in need thereof, wherein the subject's weight is decreased by inducing and/or increasing loss of fat mass while maintaining or increasing muscle mass of the subject.

177. The method or the use of any one of claims 1-175, wherein a blood glucose level of the subject is decreased following administration of a first dose of the combination therapy or of the non-naturally occurring melanocortin analog.

178. The method or the use of any one of claims 1-177, wherein the GLP-1 receptor agonist is semaglutide and the combination therapy comprising the GLP-1 receptor agonist and the non-naturally occurring melanocortin analog has an additive effect on the subject's weight loss.

179. The method or the use of claim 178, wherein the combination therapy has an additive effect on the subject's fat mass loss.

180. The method or the use of claim 282 or 283, wherein a percent lean mass of the subject is increased following administration of a first dose of the combination therapy.

181. The method or the use of claim 178, wherein the combination therapy has an additive effect on suppressing the subject's appetite

182. The method or the use of any one of claims 1-181, wherein the GLP-1 receptor agonist is a dual GLP-1/GIP receptor agonist.

183. The method or the use of claim 182, wherein the dual GLP-1/GIP receptor agonist is tirzepatide and the combination therapy has a synergistic effect on the subject's weight loss.

184. The method or the use of claim 183, wherein the combination therapy has a synergistic effect on the subject's fat mass loss.

185. The method or the use of claim 183, wherein the combination therapy has a synergistic effect on the suppressing the subject's appetite.

186. The method or the use of any one of claims 1-185, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in body weight about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

187. The method or the use of any one of claims 1-185, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 12.5%, about a 15%, about a 17.5%,

about a 20%, about a 25%, or about a 30% reduction in fat mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

188. The method or the use of any one of claims 1-185, wherein the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

189. The method or the use of any one of claims 1-185, wherein the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% increase in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

190. The method or the use of any one of claims 1-185, wherein the subject exhibits about a 5%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, about a 30%, about a 35%, about a 40%, about a 45%, about a 50%, about a 60%, or about a 70% reduction, in food intake per day about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.

191. The method or the use of any one of claims 1-185, wherein the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in blood glucose level about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy.