treats the obesity and hyperphagia associated with POMC-MC4R pathway genetic defect disorders with fewer safety issues.

SUMMARY

In one aspect, provided herein is the use of an agonist of the melanocortin-4 receptor (MC4R) in the manufacture of a medicament for treating Prader Willi Syndrome (PWS) in a subject in need thereof, wherein the medicament is to be administered at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is (R^2R^3)-A^1-$c(A^2$-A^3-A^4-A^5-A^6-A^7-A^8-$A^9)$-A^{10}-R^1 (I), wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or $(X^1, X^2, X^3, X^4, X^5)$Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-$(X^1, X^2, X^3, X^4, X^5)$Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-$N(R^4R^5)$)-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, $(C_1$-$C_{30})$alkyl, $(C_1$-$C_{30})$heteroalkyl, $(C_1$-$C_{30})$acyl, $(C_2$-$C_{30})$alkenyl, $(C_2$-$C_{30})$alkynyl, aryl$(C_1$-$C_{30})$alkyl, aryl$(C_1$-$C_{30})$acyl, substituted $(C_1$-$C_{30})$alkyl, substituted $(C_1$-$C_{30})$heteroalkyl, substituted $(C_1$-$C_{30})$acyl, substituted $(C_2$-$C_{30})$alkenyl, substituted $(C_2$-$C_{30})$alkynyl, substituted aryl$(C_1$-$C_{30})$alkyl, and substituted aryl$(C_1$-$C_{30})$acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_1-$_{10}$)alkyl, substituted ($C_{1\text{-}10}$)alkyl, ($C_{2\text{-}10}$)alkenyl, substituted ($C_{2\text{-}10}$)alkenyl, ($C_{2\text{-}10}$)alkynyl, substituted ($C_{2\text{-}10}$)alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN,

thereby treating PWS.

In another aspect, provided herein is the use of an agonist of the melanocortin-4 receptor (MC4R) in the manufacture of a medicament for treating a disorder in a subject in need thereof, wherein the medicament is to be administered at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%), wherein the disorder is chosen from:

(i) Prader Willi Syndrome (PWS);

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(viii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(ix) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the pro-hormone convertase gene;

(x) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(xi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

(xii) a disorder characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising one or more methylated cytosines, e.g., a 5'methyl cytosine); or

(xiii) a disorder characterized by a defect in the POMC-MC4R pathway other than:

(a) a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(b) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(c) a melanocortin-4 receptor (MC4R) mutation (e.g., loss of function mutation),

(d) a pro-hormone convertase mutation (e.g., loss of function mutation);

(e) a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(f) a mutation in a gene associated with Alström syndrome,

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is (R^2R^3)-A^1-*c*(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-A^{10}-R^1 (I),

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4 R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X', X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

In another aspect, provided herein is the use of an agonist of the melanocortin-4 receptor (MC4R) in the manufacture of a medicament for treating a disorder in a subject in need thereof, wherein the disorder is chosen from:

(i) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

(viii) a disorder characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine);

(ix) a disorder characterized by a defect in the POMC-MC4R pathway other than:

(a) a POMC mutation, e.g., a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(b) a leptin mutation, e.g., a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(c) a melanocortin-4 receptor (MC4R) mutation, or

(d) a prohormone convertase mutation;

(x) a disorder characterized by a homozygous POMC mutation (e.g., loss of function mutation), e.g., characterized by a POMC null genotype;

(xi) a disorder characterized by a compound heterozygous POMC mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a POMC null genotype;

(xii) a disorder characterized by a homozygous leptin mutation (e.g., loss of function mutation), e.g., characterized by a leptin null genotype;

(xiii) a disorder characterized by a compound heterozygous leptin mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a leptin null genotype,

(xiv) a disorder characterized by a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(xv) a disorder characterized by a a mutation in a gene associated with Alström syndrome,

wherein the medicament is to be administered to the subject,

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \qquad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_1-$_{10}$)alkyl, substituted ($C_{1\text{-}10}$)alkyl, ($C_{2\text{-}10}$)alkenyl, substituted ($C_{2\text{-}10}$)alkenyl, ($C_{2\text{-}10}$)alkynyl, substituted ($C_{2\text{-}10}$)alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

In another aspect, provided herein is a unit dosage of an agonist described herein, wherein the unit dosage contains 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

In an embodiment, provided herein is a method of treating Prader Willi Syndrome (PWS) in a subject in need thereof, comprising:

administering an agonist of the melanocortin-4 receptor (MC4R) at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \qquad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or $(X^1, X^2, X^3, X^4, X^5)$Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-$(X^1, X^2, X^3, X^4, X^5)$Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-

In embodiments, the presence of the predetermined sequence, e.g., mutation, is detected in the subject, and responsive to that determination, the method comprises identifying the subject as likely to respond to the agonist.

In embodiments, the subject has or is identified as having PWS.

In an embodiment, provided herein is a method of treating a disorder in a subject in need thereof, comprising:

administering an agonist of the melanocortin-4 receptor (MC4R) at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the disorder is chosen from:

(i) Prader Willi Syndrome (PWS);

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(viii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(ix) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the pro-hormone convertase gene;

(x) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(xi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

In embodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in a gene described herein) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in a POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency.

In embodiments, the presence of the hypermethylation in the POMC gene is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by a hypermethylated POMC gene, e.g., POMC deficiency.

In embodiments, the presence of the predetermined sequence, e.g., mutation, or the hypermethylation, is detected in the subject, and responsive to that determination, the method comprises identifying the subject as likely to respond to the agonist.

In embodiments, the subject has or is identified as having PWS or a disorder characterized by one or more mutations in the POMC, PCSK1, MAGEL2, leptin receptor, leptin, 5-HT2c receptor, NhHL2, pro-hormone convertase, CPE, SIM1, or other POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency.

In an embodiment, provided herein is a method of treating a disorder chosen from:

(i) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

In an embodiment, provided herein is a unit dosage of an agonist described herein, wherein the unit dosage contains 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

In embodiments, the unit dosage contains 0.5 mg of agonist.

In embodiments, the unit dosage contains 1.0 mg of agonist.

In embodiments, the unit dosage contains 1.5 mg of agonist.

In embodiments, the unit dosage is suitable for injection, e.g., subcutaneous injection.

In embodiments, the unit dosage is disposed in a delivery device suitable for injection, e.g., subcutaneous injection.

In embodiments, the unit dosage is disposed in a syringe or pen-type injector suitable for injection, e.g., subcutaneous injection.

In embodiments, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

In an embodiment, provided herein is a method of evaluating a subject, comprising:

acquiring information that identifies the subject as having or not having a predetermined sequence, e.g., mutation, in the 15q11-q13 region of chromosome 15 or in the MAGEL2 gene,

wherein identification of the subject as having the mutation identifies the patient as more likely to have improved symptoms following treatment with a MC4R agonist (e.g., a MC4R agonist described herein), and identification of the subject as not having a mutation in the 15q11-q13 region of chromosome 15 or in the MAGEL2 gene identifies the patient as being less likely to have improved symptoms following treatment with a MC4R agonist, e.g., a MC4R agonist described herein.

In another embodiment, provided herein is a method of evaluating a subject, comprising:

acquiring information that identifies the subject as having or not having a predetermined sequence, e.g., mutation, in one or more of:

the POMC gene;

the PCSK1 gene;

the MAGEL2 gene;

In embodiments, said report is in electronic, web-based, or paper form.

In embodiments, the report identifies the presence or absence of the mutation in the subject, and optionally includes an identifier for the subject from which the information was obtained.

In embodiments, the report comprises:

information on the genotype (e.g., presence or absence of the predetermined sequence, e.g., mutation) of the subject;

information on prognosis or suggested therapeutic options, e.g., MC4R agonists;

information on the likely effectiveness of a therapeutic option, e.g., MC4R agonist, the acceptability of a therapeutic option, or the advisability of applying the therapeutic option to the subject; and/or

information, or a recommendation on, the administration of the therapeutic option (e.g., MC4R agonist).

In embodiments, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

In an embodiment, provided herein is a method of selecting a subject having Prader Willi Syndrome (PWS), comprising:

acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of the paternal allele of the 15q11-q13 region of chromosome 15 or of the MAGEL2 gene;

wherein the acquiring step comprises determining the presence or absence of a predetermined sequence, e.g., mutation in the paternal allele of the 15q11-q13 region of chromosome 15 or in the MAGEL2 gene; and

wherein the presence of the predetermined sequence, e.g., mutation, identifies the subject as having PWS.

In an embodiment, provided herein is a method of selecting a subject having a POMC-MC4R pathway deficiency, comprising:

(i) acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:

the POMC gene;

CLAIMS

1. Use of an agonist of the melanocortin-4 receptor (MC4R) in the manufacture of a medicament for treating Prader Willi Syndrome (PWS) in a subject in need thereof,

wherein the medicament is to be administered at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \qquad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4 R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X', X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN,

thereby treating PWS.

2. The use of claim 1, wherein the subject has or is identified as having a loss of function mutation in the 15q11-q13 region of chromosome 15.

3. The use of claim 2, wherein the subject has or is identified as having a mutation (e.g., loss of function mutation) in the MAGEL2 gene.

4. The use of claim 1 or 2, wherein the daily dosage is 0.1 mg to 10 mg, or about 0.1 mg to about 7.5 mg, or about 0.1 mg to about 5 mg, or about 0.1 mg to about 2.5 mg, or 0.1 mg to about 2 mg, or about 0.1 mg to about 1 mg.

5. The use of any of claims 1-2, wherein the daily dosage is about 0.2 mg to about 10 mg, or about 0.2 mg to about 7.5 mg, or about 0.2 mg to about 5 mg, or about 0.2 mg to about 2.5 mg, or about 0.2 mg to about 2.5 mg, or about 0.2 mg to about 2 mg, or about 0.2 mg to about 1.5 mg, or 0.2 mg to about 1 mg.

6. The use of any of claims 1-2, wherein the daily dosage is about 0.3 mg to about 10 mg, or about 0.3 mg to about 7.5 mg, or about 0.3 mg to about 5 mg, or about 0.3 mg to about 2.5 mg, or about 0.3 mg to about 2 mg, or about 0.3 mg to about 1.5 mg, or about 0.3 mg to about 1 mg.

7. The use of any of claims 1-2, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg) to about 0.5 mg (e.g., 0.5 mg) , or about 0.5 mg (e.g., 0.5 mg) to about 0.75 mg (e.g., 0.75 mg).

8. The use of claim 7, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg), or about 0.5 mg (e.g., 0.5 mg).

9. The use of any of claims 1-2, wherein the daily dosage is about 0.75 mg (e.g., 0.75 mg) to about 1.25 mg (1.25 mg), or about 1 mg (e.g., 1 mg).

10. The use of any of claims 1-3, wherein the daily dosage is about 1.25 mg (e.g., 1.25 mg) to about 2 mg (e.g., 2 mg), or about 1.5 mg (e.g., 1.5 mg), or about 2 mg (e.g., 2 mg).

11. The use of any of the preceding claims, wherein the agonist is to be administered in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

12. The use of claim 11, wherein the unit dosage comprises one or more of the following features:

(i) it comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist; and

(ii) it is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

13. The use of any of the preceding claims, wherein the agonist is to be administered subcutaneously, e.g., by subcutaneous injection.

14. The use of any of the preceding claims, wherein the agonist is to be administered daily over a period of at least 3 weeks, e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.

15. The use of any of the preceding claims, wherein the subject;

(i) is obese, e.g., severely obese;

(ii)has early onset severe obesity;

(iii) is hyperphagic;

(iv) has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration;

(v) has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration;

(vi) has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration;

(vii) has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

16. The use of any of the preceding claims, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

17. The use of any of the preceding claims, wherein the subject has a lower body weight after administration of the agonist than before administration of the agonist.

18. The use of any of the preceding claims, wherein administration of the agonist results in one or more of:

(i) a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment;

(ii) weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer;

(iii) hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer;

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

(v) increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting);

(vi) a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week;

(vii) a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to

treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week;

(viii) a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

(ix) no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

(x) a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

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

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

19. The use of any of the preceding claims, wherein the subject is a mammal, e.g., a human.

20. The use of any of the preceding claims, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

21. The use of any of the preceding claims, comprising acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype the 15q11-q13 region of chromosome 15 or of the MAGEL2 gene.

22. The use of claim 21, wherein the agonist is to be administered in response to the detection of a predetermined sequence, e.g., a mutation, in 15q11-q13 region of chromosome 15 or in the MAGEL2 gene.

23. Use of an agonist of the melanocortin-4 receptor (MC4R) in the manufacture of a medicament for treating a disorder in a subject in need thereof,

wherein the medicament is to be administered at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the disorder is chosen from:

(i) Prader Willi Syndrome (PWS);

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(viii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(ix) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the pro-hormone convertase gene;

(x) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(xi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

(xii) a disorder characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising one or more methylated cytosines, e.g., a 5'methyl cytosine); or

(xiii) a disorder characterized by a defect in the POMC-MC4R pathway other than:

(a) a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(b) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(c) a melanocortin-4 receptor (MC4R) mutation (e.g., loss of function mutation),

(d) a pro-hormone convertase mutation (e.g., loss of function mutation);

(e) a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(f) a mutation in a gene associated with Alström syndrome,

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \qquad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4 R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

24. The use of claim 23, wherein the disorder is Prader Willi Syndrome (PWS).

25. The use of 23 or 24, wherein the subject has or is identified as having a loss of function mutation in the paternal allele of the 15q11-q13 region of chromosome 15.

26. The use of claim 24 or 25, wherein the subject has or is identified as having a mutation, e.g., loss of function mutation, in the MAGEL2 gene.

27. The use of claim 23, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene.

28. The use of any of claim 27, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional POMC allele and one non-functional POMC allele;

(ii) a homozygous carrier of the mutation(s), e.g., having a homozygous POMC null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a homozygous POMC null genotype.

29. The use of claim 23, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene.

30. The use of claim 29, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional PCSK1 allele and one non-functional PCSK1 allele.

31. The use of claim 29, wherein the subject is or is identified as being one or more of:

(i) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional PCSK1 alleles, e.g., having a PCSK1 null genotype; and

(ii) a homozygous carrier of the mutation(s), e.g., having a homozygous PCSK1 null genotype.

32. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the MAGEL2 gene.

33. The use of claim 32, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional MAGEL2 allele and one non-functional MAGEL2 allele, including the subjects where the remaining functional allele is silenced by maternal imprinting, as result of which the subject is a functional MAGEL2 null patient;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two mutated non-functional MAGEL2 alleles, e.g., having a MAGEL2 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a MAGEL2 null genotype.

34. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin receptor gene.

35. The use of any of claim 34, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional leptin receptor allele and one non-functional leptin receptor allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin receptor alleles, e.g., having a leptin receptor null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a leptin receptor null genotype.

36. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin gene.

37. The use of any of claim 36, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional leptin allele and one non-functional leptin allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin alleles, e.g., having a leptin null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a leptin null genotype.

38. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene.

39. The use of any of claim 38, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional 5-HT2c receptor allele and one non-functional 5-HT2c receptor allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional 5-HT2c receptor alleles, e.g., having a 5-HT2c receptor null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a 5-HT2c receptor null genotype.

40. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene.

41. The use of any of claim 40, wherein the subject is or is identified as being one ore more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional NhHL2 allele and one non-functional NhHL2 receptor allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional NhHL2 alleles, e.g., having a NhHL2 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a NhHL2 null genotype.

42. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the pro-hormone convertase gene.

43. The use of claim 42, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional pro-hormone convertase allele and one non-functional pro-hormone convertase allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional pro-hormone convertase alleles, e.g., having a pro-hormone convertase null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a pro-hormone convertase null genotype.

44. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene.

45. The use of any of claim 44, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional CPE allele and one non-functional CPE allele;.

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional CPE alleles, e.g., having a CPE null genotype;

(iii) a homozygous carrier of the mutation(s), e.g., having a CPE null genotype.

46. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene.

47. The use of any of claim 46, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional SIM1 allele and one non-functional SIM1 allele

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional SIM1 alleles, e.g., having a SIM1 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a SIM1 null genotype.

48. The use of claim 23, wherein the disorder is characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).

49. The use of claim 23, wherein the disorder is characterized by a defect in the POMC-MC4R pathway other than:

(a) a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(b) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(c) a heterozygous melanocortin-4 receptor (MC4R) mutation characterized by the presence of one functional MC4R allele and one non-functional MC4R allele,

(d) a pro-hormone convertase mutation (e.g., loss of function mutation);

(e) a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(f) a mutation in a gene associated with Alström syndrome.

50. The use of any of claims 23-49, wherein the daily dosage is 0.1 mg to 10 mg, or about 0.1 mg to about 7.5 mg., or 0.1 mg to about 5 mg, or about 0.1 mg to about 2.5 mg, or about 0.1 mg to about 2 mg, or is about 0.1 mg to about 1 mg.

51. The use of any of claims 23-49, wherein the daily dosage is about 0.2 mg to about 10 mg, or about 0.2 mg to about 7.5 mg, or about 0.2 mg to about 5 mg, or about 0.2 mg to about 2.5 mg, or about 0.2 mg to about 2 mg, or about 0.2 mg to about 1.5 mg, or about 0.2 mg to about 1 mg.

52. The use of any of claims 23-49, wherein the daily dosage is about 0.3 mg to about 10 mg, or about 0.3 mg to about 7.5 mg, or about 0.3 mg to about 5 mg, or about 0.3 mg to about 2.5 mg, or about 0.3 mg to about 2 mg, or about 0.3 mg to about 1.5 mg, or about 0.3 mg to about 1 mg.

53. The use of any of claims 23-49, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg) to about 0.5 mg (e.g., 0.5 mg), or about 0.5 mg (e.g., 0.5 mg) to about 0.75 mg (e.g., 0.75 mg).

54. The use of claim 53, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg), or about 0.5 mg (e.g., 0.5 mg).

55. The use of any of claims 23-49, wherein the daily dosage is about 0.75 mg (e.g., 0.75 mg) to about 1.25 mg (1.25 mg).

56. The use of claim 55, wherein the daily dosage is about 1 mg (e.g., 1 mg).

57. The use of any of claims 23-49, wherein the daily dosage is about 1.25 mg (e.g., 1.25 mg) to about 2 mg (e.g., 2 mg).

58. The use of claim 57, wherein the daily dosage is about 1.5 mg (e.g., 1.5 mg) or about 2 mg (e.g., 2 mg).

59. The use of any of claims 23-58, wherein the agonist is to be administered in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject, wherein the unit dosage:

(i) comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist; or

(ii) is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

60. The use of any of claims 23-59, wherein the agonist is to be administered subcutaneously, e.g., by subcutaneous injection.

61. The use of any of claims 23-60, wherein the agonist is to be administered daily over a period of at least 3 weeks, e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.

62. The use of any of claims 23-61, wherein the subject:

(i) is obese, e.g., severely obese;

(ii) has early onset severe obesity

(iii) is hyperphagic;

(iv) has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration;

(v) has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration;

(vi) has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration; or

(vii) has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

63. The use of any of claims 23-62, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

64. The use of any of claims 23-63, wherein the subject has a lower body weight after administration of the agonist than before administration of the agonist.

65. The use of any of claims 23-64, wherein administration of the agonist results in one or more of:

(i) a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment;

(ii) weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer;

(iii) hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer;

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

(v) an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the

REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting);

(vi) a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week;

(vii) a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week;

(viii) a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

(ix) no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

(x) a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

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

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

66. The use of any of claims 23-65, wherein the subject is a mammal, e.g., a human.

67. The use of any of claims 23-66, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

68. The use of any of claims 23-66, comprising acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:

the POMC gene;the prohormone convertase gene, including the PCSK1 gene;
the MAGEL2 gene;
the leptin receptor gene;
the leptin gene;
the 5-HT2c receptor gene;
the nescient helix loop helix 2 (NhHL2) gene;
the carboxypeptidase E (CPE) gene;
the single-minded 1 (SIM1) gene;
a POMC-MC4R pathway gene;
BBS1-BBS20);
ALMS1,
BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, NROB2, and 16p11.2 deletions (including the SH2B1 gene).

69. The use of claim 68, wherein the agonist is to be administered in response to the detection of a predetermined sequence, e.g., a mutation, in a gene in claim 68.

70. Use of an agonist of the melanocortin-4 receptor (MC4R) in the manufacture of a medicament for treating a disorder in a subject in need thereof, wherein the disorder is chosen from:

(i) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

(viii) a disorder characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine);

(ix) a disorder characterized by a defect in the POMC-MC4R pathway other than:

(a) a POMC mutation, e.g., a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(b) a leptin mutation, e.g., a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(c) a melanocortin-4 receptor (MC4R) mutation, or

(d) a prohormone convertase mutation;

(x) a disorder characterized by a homozygous POMC mutation (e.g., loss of function mutation), e.g., characterized by a POMC null genotype;

(xi) a disorder characterized by a compound heterozygous POMC mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a POMC null genotype;

(xii) a disorder characterized by a homozygous leptin mutation (e.g., loss of function mutation), e.g., characterized by a leptin null genotype;

(xiii) a disorder characterized by a compound heterozygous leptin mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a leptin null genotype,

(xiv) a disorder characterized by a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(xv) a disorder characterized by a a mutation in a gene associated with Alström syndrome,

wherein the medicament is to be administered to the subject,

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

(R^2R^3)-A^1-*c*(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-A^{10}-R^1 (I),

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

71. The use of claim 70, wherein the disorder is characterized by one or more of:

(i) a homozygous POMC mutation (e.g., loss of mutation), e.g., characterized by a POMC null genotype; and

(ii) compound heterozygous POMC mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a POMC null genotype.

72. The use of claim 71, wherein the mutations are p.Lys51Term g.A6851>T and p.Arg145ProfsX12 g.7134delG.

73. The use of claim 70, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene.

74. The use of claim 73, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional PCSK1 allele and one non-functional PCSK1 allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional PCSK1 alleles, e.g., having a PCSK1 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a PCSK1 null genotype.

75. The use of claim 70, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the MAGEL2 gene.

76. The use of claim 75, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional MAGEL2 allele and one non-functional MAGEL2 allele, including the subjects where the remaining functional allele is silenced by maternal imprinting, as result of which the subject is a functional MAGEL2 null patient;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional MAGEL2 alleles, e.g., having a MAGEL2 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a MAGEL2 null genotype.

77. The use of claim 70, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin receptor gene.

78. The use of any of claim 77, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional leptin receptor allele and one non-functional leptin receptor allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin receptor alleles, e.g., having a leptin receptor null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a leptin receptor null genotype.

79. The use of claim 70, wherein the disorder is characterized by a homozygous leptin mutation (e.g., loss of mutation), e.g., characterized by a leptin null genotype.

80. The use of claim 70, wherein the disorder is characterized by a compound heterozygous leptin mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a leptin null genotype.

81. The use of claim 70, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene.

82. The use of any of claim 81, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional 5-HT2c receptor allele and one non-functional 5-HT2c receptor allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional 5-HT2c receptor alleles, e.g., having a 5-HT2c receptor null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a 5-HT2c receptor null genotype.

83. The use of claim 70, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene.

84. The use of any of claim 83, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional NhHL2 allele and one non-functional NhHL2 receptor allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional NhHL2 alleles, e.g., having a NhHL2 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a NhHL2 null genotype.

85. The use of claim 70, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene.

86. The use of any of claim 85, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional CPE allele and one non-functional CPE allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional CPE alleles, e.g., having a CPE null genotype;

(iii) a homozygous carrier of the mutation(s), e.g., having a CPE null genotype.

87. The use of claim 70, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene.

88. The use of any of claim 87, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional SIM1 allele and one non-functional SIM1 allele

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional SIM1 alleles, e.g., having a SIM1 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a SIM1 null genotype.

89. The use of claim 70, wherein the disorder is characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).

90. The use of claim 89, wherein the subject has or is identified as having a hypermethylated CpG island in the POMC gene, e.g., at the intron2-exon3 boundary of the POMC gene.

91. The use of claim 70, wherein the disorder is characterized by a defect in the POMC-MC4R pathway other than:

(a) a POMC mutation, e.g., a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele;.

(b) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele;

(c) a heterozygous melanocortin-4 receptor (MC4R) mutation characterized by the presence of one functional MC4R allele and one non-functional MC4R allele;

(d) a pro-hormone convertase mutation (e.g., loss of function mutation);

(e) a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(f) a mutation in a gene associated with Alström syndrome.

92. The use of any of claims 70-91, wherein the agonist is to be administered in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject, wherein the unit dosage:

(i) comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist; or

(ii) is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

93. The use of any of claims 70-92, wherein the agonist is to be administered subcutaneously, e.g., by subcutaneous injection.

94. The use of any of claims 70-93, wherein the agonist is to be administered daily over a period of at least 3 weeks, e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.

95. The use of any of claims 70-94, wherein the subject:

(i) is obese, e.g., severely obese

(ii) has early onset severe obesity

(iii) is hyperphagic

(iv) has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration;

(v) has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration;

(vi) has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration; or

(vii) has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

96. The use of any of claims 70-95, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

97. The use of any of claims 70-96, wherein the subject has a lower body weight after administration of the agonist than before administration of the agonist.

98. The use of any of claims 70-97, wherein administration of the agonist results in one or more of:

(i) a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks

of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment;

(ii) weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer;

(iii) hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer;

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

(v) an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting);

(vi) a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week;

(vii) a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week;

(viii) a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

(ix) no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

(x) a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;

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

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

99. The use of any of claims 70-98, wherein the subject is a mammal, e.g., a human.

100. The use of any of claims 70-99, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

101. The use of any of claims 70-100, comprising acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:

the POMC gene;

the PCSK1 gene;

the MAGEL2 gene;

the leptin receptor gene;

the leptin gene;
the 5-HT2c receptor gene;
the nescient helix loop helix 2 (NhHL2) gene;
the carboxypeptidase E (CPE) gene;
the single-minded 1 (SIM1) gene.;
any of the BBS1-BBS20 genes;
the ALMS1 gene,
or the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).

102. The use of claim 101, wherein the agonist is to be administered in response to the detection of a predetermined sequence, e.g., a mutation, in a gene in claim 239.

103. The use of any of claims 70-100, comprising acquiring knowledge of the state of methylation of the POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).

104. The use of claim 103, wherein the agonist is to be administered in response to the detection of hypermethylation.

105. A unit dosage of an agonist described herein, wherein the unit dosage contains 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

106. The unit dosage of claim 105, disposed in a delivery device, e.g., a syringe, suitable for injection, e.g., subcutaneous injection.

107. The unit dosage of any of claims 105-106, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

108. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in a BBS1-19, or 20 gene.

109. The use of claim 108, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional BBS1-19, or 20 allele and one non-functional BBS1-19, or 20 allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional BBS1-19, or 20 alleles, e.g., having a BBS1-19, or 20 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having a BBS1-19, or 20 null genotype.

110. The use of claim 23, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in an ALMS1 gene.

111. The use of claim 110, wherein the subject is or is identified as being one or more of:

(i) a heterozygous carrier of the mutation(s), e.g., having one functional ALMS1 allele and one non-functional ALM1 allele;

(ii) a compound heterozygous carrier of the mutation(s), e.g., having two non-functional ALMS1 alleles, e.g., having an ALMS1 null genotype; and

(iii) a homozygous carrier of the mutation(s), e.g., having an ALMS1 null genotype.

112. The use of claim 23, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).

113. The use of claim 107, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional allele and one non-functional allele of the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).

114. The use of claim 107, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional alleles, e.g., having a null genotype, of of the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).