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

SUMMARY

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^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.

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 a disorder in a subject in need thereof, wherein the melanocortin-4 receptor (MC4R) is to be administered at a daily dosage of 0.1 mg (e.g., 0.1 mg +/- 5%) to 10 mg (e.g., 10 mg +/- 5%);

wherein the disorder is chosen from:

(i) a disorder characterized by one or more mutations in the POMC gene;

(ii) a disorder characterized by one or more mutations in the PCSK1 gene;

(iii) a disorder characterized by one or more mutations in the leptin receptor gene;

(iv) a disorder characterized by one or more mutations in the leptin gene;

(v) a disorder characterized by one or more mutations in the MAGEL2 gene;

(vi) a disorder characterized by one or more mutations in the 5-HT2c receptor gene;

(vii) a disorder characterized by one or more mutations in the nescient helix loop helix 2 (NhHL2) gene;

(viii) a disorder characterized by one or more mutations in a pro-hormone convertase gene;

(ix) a disorder characterized by one or more mutations in the carboxypeptidase E (CPE) gene; and

(x) a disorder characterized by one or more mutations in the single-minded 1 (SIM1) gene;

wherein the agonist is a MC4R agonist having a structure of Formula (I) 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 His, 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^1, X^2, X^3, X^4, and X^5 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 an embodiment, 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, $(C_{1\text{-}10})$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 embodiment, 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^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 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 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^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-

CLAIMS

1. 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 melanocortin-4 receptor (MC4R) is to be administered at a daily dosage of 0.1 mg (e.g., 0.1 mg +/- 5%) to 10 mg (e.g., 10 mg +/- 5%);

wherein the disorder is chosen from:

(i) a disorder characterized by one or more mutations in the POMC gene;

(ii) a disorder characterized by one or more mutations in the PCSK1 gene;

(iii) a disorder characterized by one or more mutations in the leptin receptor gene;

(iv) a disorder characterized by one or more mutations in the leptin gene;

(v) a disorder characterized by one or more mutations in the MAGEL2 gene;

(vi) a disorder characterized by one or more mutations in the 5-HT2c receptor gene;

(vii) a disorder characterized by one or more mutations in the nescient helix loop helix 2 (NhHL2) gene;

(viii) a disorder characterized by one or more mutations in a pro-hormone convertase gene;

(ix) a disorder characterized by one or more mutations in the carboxypeptidase E (CPE) gene; and

(x) a disorder characterized by one or more mutations in the single-minded 1 (SIM1) gene;

wherein the agonist is a MC4R agonist having a structure of Formula (I) 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 His, 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^1, X^2, X^3, X^4, and X^5 each is, independently for each occurrence, H, F, Cl, Br, I, ($C_{1\text{-}10}$)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.

2. The use of claim 1, wherein the disorder is chosen from:

(i) a disorder characterized by one or more mutations in the POMC gene;

(ii) a disorder characterized by one or more mutations in the PCSK1 gene; and

(iii) a disorder characterized by one or more mutations in the leptin receptor gene.

3. The use of any one of claims 1-2, wherein the subject has or is identified as being:

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

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

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

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

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

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

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

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

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

4. The use of any one of the preceding claims, wherein the subject has or is identified as having a loss of function mutation in the 15q11-q13 region of chromosome 15.

5. The use of any one of the preceding claims, wherein the subject has or is identified as having 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).

6. The use of any one 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;

(viii) 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; or

(ix) has a lower body weight after administration of the agonist than before administration of the agonist.

7. The use of any one of the preceding claims, wherein the subject has a body mass index (BMI) greater than 35 kg/m^2 prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration; or

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 1 kg to 3 kg after 1 week of treatment, or 1 kg to 6 kg after 2 weeks of treatment, or 2 kg to 12 kg after 4 weeks of treatment, or 4 kg to 24 kg after 8 weeks of treatment, or 8 kg to 48 kg after 16 weeks of treatment;

(ii) weight loss in the subject at a rate of 1-2 kg/week, e.g., 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) 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 pressure 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;

thereby treating a disorder in a subject in need thereof.

8. The use of any one of the preceding claims, wherein the daily dosage is 0.1 mg to 10 mg.

9. 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.

10. The use of claim 9, wherein the unit dosage comprises 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 mg of the agonist.

11. The use of any one of claims 9-10, wherein the unit dosage is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe), an implantable device, a needleless hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

12. The use of any one of claims 1-11, wherein the agonist is to be administered orally or parenterally (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, extended release, slow release implant, depot and the like).

13. The use of any one of the preceding claims, wherein the agonist is a compound of Formula I, wherein:

A^1 is A6c, Arg, D-Arg, Cha, D-Cha, hCha, Chg, D-Chg, Gaba, Ile, Leu, hLeu, Met, β-hMet, 2-Nal, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, Val, or deleted;

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

A^3 is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, D-Glu, Gly, D-Ile, D-Leu, D-Tle, D-Val, or deleted;

A^4 is His or 3-Pal;

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

A^6 is Arg, or hArg;

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

A^8 is A6c, D-Ala, Aha, Ahx, Ala, β-Ala, Apn, Gaba, Gly or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen; and

A^{10} is Thr, or deleted,

wherein at least one of A^3 or A^8 is deleted, but not both, or pharmaceutically acceptable salts thereof.

14. The use of any one 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).

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