

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

To: Hannah R. Koyfman
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Date of mailing
(day/month/year)

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Applicant's or agent's file reference
R2054-7024WO

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US21/52032

International filing date (day/month/year)

24 September 2021 (24.09.2021)

Priority date (day/month/year)

24 September 2020 (24.09.2020)

International Patent Classification (IPC) or both national classification and IPC

IPC = A61P 3/04; A61K 38/08; C07K 14/685 (2021.01)

CPC = A61P 3/04; A61K 38/08; C07K 14/685

Applicant RHYTHM PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US
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Date of completion of this opinion

02 February 2022 (02.02.2022)

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(b)).
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
 - ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
-***-Please See Supplemental Page-***-

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. -***-Please See Supplemental Page-***-

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6, 10, 13-15, 21, 23, 25-28, 32-44	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	21, 23, 25-28	YES
	Claims	1-6, 10, 13-15, 32-44	NO
Industrial applicability (IA)	Claims	1-6, 10, 13-15, 21, 23, 25-28, 32-44	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-6, 10, and 13 lack an inventive step under PCT Article 33(3) as being obvious over US 2018/0311309 A1 (RHYTHM PHARMACEUTICALS, INC.) (hereinafter 'Rhythm') in view of the publication entitled 'Molecular Analysis of Bardet-Biedl Syndrome Families: Report of 21 Novel Mutations in 10 Genes' by Chen et al. (hereinafter 'Chen') as evidenced by the publication entitled 'Bardet-Biedl syndrome: Genetics, molecular pathophysiology, and disease management' by Priya et al. (hereinafter 'Priya').

As per claim 1, Rhythm discloses a method of treating a disease, disorder, or condition in a subject (treating a subject with Bardet-Biedl syndrome; paragraphs [0554], [0633], [0650]) comprising administering to the subject a melanocortin-4 receptor (MC4R) agonist (administering a MC4R agonist; paragraphs [0554], [0633]), wherein the disease, disorder, or condition is related to an MC4R pathway agonizable gene ARL6 selected from a long list (where Bardet-Biedl syndrome is associated with BBS1-BBS20, where BBS3 (ARL6) is one of those genes; paragraphs [0632]-[0633]). Rhythm does not disclose wherein the disease, disorder, or condition is related to an MC4R pathway agonizable gene ARL6. Chen discloses a disease, disorder, or condition is related to an MC4R pathway agonizable gene ARL6 (individuals with Bardet-Biedl syndrome have BBS3 mutations; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the MC4R pathway agonizable gene ARL6 selected from a long list, as previously disclosed by Rhythm, with a disease, disorder, or condition is related to an MC4R pathway agonizable gene ARL6, as previously disclosed by Chen, for a superior method which provides the benefit of targeting conditions associated with ARL6 which is prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

As per claim 2, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the disease, disorder, or condition is characterized by a mutation, e.g., a substitution mutation, a deletion mutation, or a polymorphism, in the MC4R pathway agonizable gene selected from a long list (Bardet-Biedl syndrome is associated with mutations in BBS1-BBS20; paragraphs [0632]-[0633]). Rhythm does not disclose the MC4R pathway agonizable gene. Chen discloses wherein the disease, disorder, or condition is characterized by a mutation, e.g., a substitution mutation, a deletion mutation, or a polymorphism, in the MC4R pathway agonizable gene (individuals with Bardet-Biedl syndrome have BBS3 mutations; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the MC4R pathway agonizable gene ARL6 selected from a long list, as previously disclosed by Rhythm, with a disease, disorder, or condition is characterized by a mutation in the MC4R pathway agonizable gene ARL6, as previously disclosed by Chen, for a superior method which provides the benefit of targeting conditions associated with ARL6 mutations which are prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

As per claim 3, Rhythm and Chen, in combination, disclose the method of claim 2, and Rhythm further discloses wherein the subject is homozygous or heterozygous for the mutation in the MC4R pathway agonizable gene, selected from a long list (a mutation in BBS1-19 where the subject is a homozygous or heterozygous carrier for the mutation; paragraph [0633]; claims 251-254). Rhythm does not disclose the mutation in the MC4R pathway agonizable gene. Chen discloses the MC4R agonizable gene mutations (individuals with Bardet-Biedl syndrome have BBS3 mutations; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the mutation in the MC4R pathway agonizable gene selected from a long list, as previously disclosed by Rhythm, with the mutation in the MC4R pathway agonizable gene, as previously disclosed by Chen, for a superior method which provides the benefit of targeting conditions associated with ARL6 mutations which are prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

As per claim 4, Rhythm and Chen, in combination, disclose the method of claim 2, and Rhythm further discloses 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 MC4R pathway agonizable gene, selected from a long list (a mutation in BBS1-19 where the subject is a heterozygous carrier for the mutation; paragraph [0633]; claims 251-252). Rhythm does not disclose the mutation(s) of the MC4R pathway agonizable gene. Chen discloses the MC4R agonizable gene mutations (individuals with Bardet-Biedl syndrome have BBS3 mutations; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the heterozygous carrier of the mutations in the MC4R pathway agonizable gene selected from a long list, as previously disclosed by Rhythm, with the MC4R pathway agonizable gene mutations, as previously disclosed by Chen, for a superior method which provides the benefit of

---Continued in Supplemental Box---

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
Claim 35 is objected to under PCT Rule 66.2(a)(iii) because it is missing a period.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

---Continued From Box IV (ii): Lack of unity of invention---

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups 1+, Claims 1-44, and ARL6 (MC4R pathway agonizable gene), Bardet-Biedl syndrome (disease), Acc (A1), Cys (A2), Gly (A3), His (A4), D-Phe (A5), Arg (A6), Trp (A7), Gly (A8), Cys (A9), Acc (A10), OH (R1), H (R2), H (R3) are directed towards methods of treating a disease, disorder, or condition comprising administering an MC4R agonist.

The methods of Claims 1-6 (each in-part), 10 (in-part), 13-15 (each in-part), 21 (in-part), 23 (in-part), 25-28 (in-part), 32-44 (each in-part) are believed to encompass the first named invention of Groups 1+ and are the claims that will be searched without fee to the extent that they encompass ARL6 (first exemplary MC4R pathway agonizable gene), Bardet-Biedl syndrome (first exemplary disease), Acc (first exemplary A1), Cys (first exemplary A2), Gly (first exemplary A3), His (first exemplary A4), D-Phe (first exemplary A5), Arg (first exemplary A6), Trp (first exemplary A7), Gly (first exemplary A8), Cys (first exemplary A9), Acc (first exemplary A10), OH (first exemplary R1), H (first exemplary R2), H (first exemplary R3).

Applicant is invited to elect additional MC4F pathway agonizable gene(s), disease(s), A1(s), A2(s), A3(s), A4(s), A5(s), A6(s), A7(s), A8(s), A9(s), A10(s), R1(s), R2(s), R3(s) such that each elected species is fully specified (i.e. no optional or variable amino acids, groups, or substituents), and where available as an option within at least one searchable claim, to be searched. Additional MC4F pathway agonizable gene(s), disease(s), A1(s), A2(s), A3(s), A4(s), A5(s), A6(s), A7(s), A8(s), A9(s), A10(s), R1(s), R2(s), R3(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected MC4F pathway agonizable gene(s), disease(s), A1(s), A2(s), A3(s), A4(s), A5(s), A6(s), A7(s), A8(s), A9(s), A10(s), R1(s), R2(s), R3(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. Exemplary elections would be RAI1 (MC4F pathway agonizable gene); Alstrom Syndrome (disease); or HN-(CH₂)_m-C(O) where m is 1 (A1), D-Cys (A2), Ala (A3), 2-Pal (A4), Phe (A5), hArg (A6), 1-Nal (A7), D-Ala (A8), D-Cys (A9), HN-(CH₂)_t-C(O) where t is 1 (A10), NH₂ (R1), (C1-C30)alkyl (R2), (C1-C30)alkyl (R3).

Even if Groups 1+ were considered to share the technical features including: a method of treating a disease, disorder, or condition in a subject comprising administering to the subject a melanocortin-4 receptor "MC4R" agonist, wherein the disease, disorder, or condition is related to an MC4R pathway agonizable gene selected from ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A4, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, TRPC5, PHIP, and MeCP2; these shared technical features are previously disclosed by the publication entitled 'Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome' by Haws et al. (hereinafter 'Haws').

Haws discloses a method of treating a disease, disorder, or condition in a subject (a method of treating Bardet-Biedl syndrome in individuals; abstract) comprising administering to the subject a melanocortin-4 receptor "MC4R" agonist (administering setmelanotide which is an MCR4 agonist; abstract; page 2134, first column, third paragraph), wherein the disease, disorder, or condition is related to an MC4R pathway agonizable gene selected from ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A4, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, TRPC5, PHIP, and MeCP2 (the Bardet-Biedl syndrome is related to BBS1-21 (BBS19, BBS21); page 2134, first column, first paragraph).

Since none of the special technical features of the Groups 1+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Haws reference, unity of invention is lacking.

---Continued From Box IV (iii)---

Groups 1+, Claims 1-44, and ARL6 (MC4R pathway agonizable gene), Bardet-Biedl syndrome (disease), Acc (A1), Cys (A2), Gly (A3), His (A4), D-Phe (A5), Arg (A6), Trp (A7), Gly (A8), Cys (A9), Acc (A10), OH (R1), H (R2), H (R3)

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Continued From Box V. 2: Citations and Explanations-

targeting conditions associated with ARL6 mutations which are prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

As per claim 5, Rhythm and Chen, in combination, disclose the method of claim 2, and Rhythm further discloses wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two distinct non-functional alleles, e.g., having the MC4R pathway agonizable gene, selected from a long list (mutations in BBS1-19 where the subject is a compound heterozygous carrier for the mutations; paragraph [0633]; claims 251, 253). Rhythm does not disclose the mutation(s) of the MC4R pathway agonizable gene. Chen discloses the MC4R agonizable gene mutations (individuals with Bardet-Biedl syndrome have BBS3 mutations including a T31M mutation or a novel c.123+1118del 53,985 mutation; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound heterozygous carrier of the mutations in the MC4R pathway agonizable gene selected from a long list, as previously disclosed by Rhythm, with the MC4R pathway agonizable gene mutations, as previously disclosed by Chen, for a superior method which provides the benefit of targeting conditions associated with ARL6 mutations which are prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

As per claim 6, Rhythm and Chen, in combination, disclose the method of claim 2, and Rhythm further discloses wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a homozygous null genotype of the MC4R pathway agonizable gene, selected from a long list (a mutation in BBS1-19 where the subject is a heterozygous carrier for the mutation; paragraph [0633]; claims 251, 254). Rhythm does not disclose the mutation(s) of the MC4R pathway agonizable gene. Chen discloses the MC4R agonizable gene mutations (individuals with Bardet-Biedl syndrome have BBS3 mutations including a T31M mutation or a novel c.123+1118del 53,985 mutation; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the homozygous carrier of the mutations in the MC4R pathway agonizable gene selected from a long list, as previously disclosed by Rhythm, with the MC4R pathway agonizable gene mutations, as previously disclosed by Chen, for a superior method which provides the benefit of targeting conditions associated with ARL6 mutations which are prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

As per claim 10, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the disease, disorder, or condition is characterized by a plurality of mutations, e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 mutations, in the MC4R pathway agonizable gene selected from a long list (a compound heterozygous carrier of mutations in BBS1-19, with two functional alleles with different mutations; paragraph [0633]; claims 251, 253). Rhythm does not disclose mutations in the MC4R pathway agonizable gene. Chen discloses mutations in the MC4R pathway agonizable gene (individuals with Bardet-Biedl syndrome have BBS3 mutations including a T31M mutation or a novel c.123+1118del 53,985 mutation; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the mutations in the MC4R pathway agonizable gene selected from a long list, as previously disclosed by Rhythm, with mutations in the MC4R pathway agonizable gene, as previously disclosed by Chen, for a superior method which provides the benefit of targeting conditions associated with ARL6 mutations which are prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

As per claim 13, Rhythm and Chen, in combination, disclose the method of claim 1, wherein the disease, disorder, or condition is characterized by modulation, e.g., upregulation or downregulation, of the MC4R pathway agonizable gene selected from a long list (Bardet-Biedl syndrome is associated with BBS1-BBS20 mutations including non-coding mutations (downregulation); paragraph [0632]-[0633]). Rhythm does not disclose the MC4R pathway agonizable gene. Chen discloses the MC4R pathway agonizable gene (individuals with Bardet-Biedl syndrome have BBS3 mutations; abstract; page 5321, first column, second paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the MC4R pathway agonizable gene selected from a long list, as previously disclosed by Rhythm, with the MC4R pathway agonizable gene, as previously disclosed by Chen, for a superior method which provides the benefit of targeting conditions associated with ARL6 which is prevalent in Asian populations (Chen reference; page 5321, first column, second paragraph; as indicated by the Priya reference; page 621, first column, first paragraph).

Claims 14-15, 32-44 lack an inventive step under PCT Article 33(3) as being obvious over Rhythm in view of Chen.

As per claim 14, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the disease, disorder, or condition comprises Bardet-Biedl syndrome (treating Bardet-Biedl syndrome; paragraphs [0650]).

As per claim 15, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the disease, disorder, or condition comprises Bardet-Biedl syndrome (treating Bardet-Biedl syndrome; paragraphs [0650]).

As per claim 32, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ "SEQ ID NO: 140" (the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH₂ which is SEQ ID NO: 140, where SEQ ID NO: 140 of the instant PCT application is 100% identical to SEQ ID NO: 140 of the Rhythm reference; paragraph [0808]).

As per claim 33, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the MC4R agonist is formulated as a pharmaceutical composition (the MC4R agonist is formulated as a pharmaceutical composition; paragraph [1040]).

Continued Within the Next Supplemental Box-

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Continued from previous Supplemental Box-

As per claim 34, Rhythm and Chen, in combination, disclose the method of claim 33, and Rhythm further discloses wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient (the pharmaceutical formulation comprises an excipient; paragraphs [1040], [1042]).

As per claim 35, Rhythm and Chen, in combination, disclose the method of claim 33, and Rhythm further discloses wherein the pharmaceutical composition comprises a polyethylene glycol, e.g., a modified polyethylene glycol, e.g., mPEG-DSPE, e.g., mPEG-2,000-DSPE (the pharmaceutical formulation comprises polyethylene glycol; paragraphs [1040], [1042]).

As per claim 36, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses comprising administering the MC4R agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject (administering the MC4R in a unit dosage suitable for injection to the subject; paragraphs [0583], [1039]).

As per claim 37, Rhythm and Chen, in combination, disclose the method of claim 36, and Rhythm further discloses wherein the unit dosage form is disposed within a delivery device, e.g., a syringe, e.g., prefilled syringe, an implantable device, a needleless hypodermic injection device, an infusion pump, e.g., implantable infusion pump, or an osmotic delivery system (the unit dosage is disposed within a delivery device suitable for injection, where the device is a syringe; paragraph [1039]).

As per claim 38, Rhythm and Chen, in combination, disclose the method of claim 37, and Rhythm further discloses wherein the MC4R agonist is administered subcutaneously, e.g., by subcutaneous injection (the MC4R agonist is administered via subcutaneous injection; paragraph [1044]).

As per claim 39, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the subject is obese, e.g., severely obese (the subject is obese or severely obese; paragraph [0679]).

As per claim 40, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the subject is hyperphagic (the subject is hyperphagic; paragraph [0679]).

As per claim 41, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the subject has a body mass index "BMI" greater than 35 kg/m², e.g., 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m² or greater, prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration (the subject is obese with a BMI greater than 35 kg/m²; paragraphs [0561], [0679]-[0680]).

As per claim 42, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the subject has a body mass index "BMI" greater than 40 kg/m², e.g., 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m² or greater, prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration (the subject is severely obese with a BMI greater than 40 kg/m²; paragraphs [0561], [0679]-[0680]).

As per claim 43, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration (the subject has failed one or more previous therapies such as exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist; paragraphs [0342], [0554]).

As per claim 44, Rhythm and Chen, in combination, disclose the method of claim 1, and Rhythm further discloses wherein the subject has a lower body weight after administration of the MC4R agonist than before administration of the MC4R agonist (the subject has a lower body weight after administration of the MC4R agonist than before administration of the MC4R agonist; paragraphs [0343], [0554]).

Claims 21, 23, and 25-28 meet the criteria set out in PCT Article 33(2)-(3).

Claim 21 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest MC4R agonists with a structure formula of (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1, where A3 is Gly, A4 is His, A5 is D-Phe, A6 is Arg, A7 is Trp.

Rhythm discloses wherein the MC4R agonist has the structure of formula I): (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1 I) (the MC4R agonist has the structure of (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1; paragraph [0767]), wherein: A1 is Acc (A1 is Acc; paragraph [0769]), A2 is Cys (A2 is Cys; paragraphs [0770], [0791]), A3 is Gly selected from a long list (A3 is Gly; paragraph [0771]), A4 is His selected from a long list (A4 is His; paragraph [0772]), A5 is D-Phe selected from a long list (A5 is D-Phe; paragraph [0773]), A6 is Arg selected from a long list (A6 is Arg; paragraph [0774]), A7 is Trp selected from a long list (A7 is Trp; paragraph [0775]), A8 is Gly (A8 is Gly; paragraphs [0776], [0793]), A9 is Cys (A9 is Cys; paragraphs [0777], [0791]), A10 is Acc (A10 is Acc; paragraph [0778]), R1 is OH (R1 is OH; paragraph [0779]), each of R2 and R3 is H (each of R2 and R3 is H; paragraph [0780], [0794]). Rhythm does not disclose A3 is Gly, A4 is His, A5 is D-Phe, A6 is Arg, A7 is Trp.

WO 2007/008704 A2 (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES S.A.S.) (hereinafter 'SCR') discloses a MC4R agonist has the structure of formula I): (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1 I) (a MC4R agonist with the structure of (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1; page 7, second-fifteenth paragraphs), wherein: A1 is Acc (A1 is Acc; page 7, second-fifteenth paragraphs), A2 is Cys (A2 is Cys; page 7, second-fifteenth paragraphs; page 8, item IV), A3 is Gly selected from a long list (A3 is Gly; page 7, second-fifteenth paragraphs), A4 is His selected from a long list (A4 is His; page 7, second-fifteenth paragraphs), A5 is D-Phe selected from a long list (A5 is D-Phe; page 7, second-fifteenth paragraphs), A6 is Arg selected from a long list (A6 is Arg; page 7, second-fifteenth paragraphs), A7 is Trp selected from a long list (A7 is Trp; page 7, second-fifteenth paragraphs), A8 is Gly (A8 is Gly;

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US21/52032

Supplemental Box

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paragraphs [0776], [0793]), A9 is Cys (A9 is Cys; page 7, second-fifteenth paragraphs; page 8, item IV), A10 is Acc (A10 is Acc; page 7, second-fifteenth paragraphs), R1 is OH (R1 is OH; page 7, second-fifteenth paragraphs), each of R2 and R3 is H (each of R2 and R3 is H; page 7, second-fifteenth paragraphs; page 8, item VII). SCR does not disclose A3 is Gly, A4 is His, A5 is D-Phe, A6 is Arg, A7 is Trp.

The publication entitled 'Hydrogen cyanide synthase subunit HcnC precursor [Planctomycetes bacterium Pan189]' to GenPept (hereinafter 'GenPept') discloses A2-A3-A4-A5-A6-A7-A8; wherein A2 is Cys, A3 is Gly, A4 is His, A5 is Phe, A6 is Arg, A7 is Trp, A8 is Gly (A2-A8 are identical to residues 324-330 of the GenPept sequence; pages 1-2). GenPept does not disclose the MC4R agonist is has the structure of formula I): (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1 I), wherein: A1 is Acc, A2 is Cys, A3 is Gly, A4 is His, A5 is D-Phe, A6 is Arg, A7 is Trp, A8 is Gly, A9 is Cys, A10 is Acc, R1 is OH, each of R2 and R3 is H.

Chen discloses, in-part, the method of claim 1. Chen does not disclose wherein the MC4R agonist is has the structure of formula I): (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1 I), wherein: A1 is Acc, A2 is Cys, A3 is Gly, A4 is His, A5 is D-Phe, A6 is Arg, A7 is Trp, A8 is Gly, A9 is Cys, A10 is Acc, R1 is OH, each of R2 and R3 is H.

Rhythm, SCR, GenPept, and Chen, either alone or in combination, fail to disclose MC4R agonists with a structure formula of (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1, where A3 is Gly, A4 is His, A5 is D-Phe, A6 is Arg, A7 is Trp. While Rhythm and SCR disclose MC4R agonists with a structure formula of (R2R3)-A1-c(A2-A3-A4-A5-A6-A7-A8-A9)-A10-R1, where A3 is Gly, A4 is His, A5 is D-Phe, A6 is Arg, A7 is Trp, those residues are selected from long lists and they do not have a specific disclosure of the required residues in one compound and as such, selecting the required residues each from a long list, would not have been obvious without the benefit of impermissible hindsight. While GenPept discloses A2 is Cys, A3 is Gly, A4 is His, A5 is Phe, A6 is Arg, A7 is Trp, A8 is Gly, this disclosure is part of a longer sequence of a bacterium protein and is not used as a MC4R agonist, and would not have been obvious to have combined with the disclosures of Rhythm or SCR without the benefit of impermissible hindsight.

Claims 23 and 25-28 meet the criteria set out in PCT Article 33(2)-(3), because they depend on claim 21.

Claims 1-6, 10, 13-15, 21, 23, 25-28, and 32-44 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.