

CLAIMS

[Claim 1] A GIP receptor agonist peptide represented by formula (I):

P¹-Tyr-A2-Glu-Gly-Thr-Phe-Ile-Ser-A9-Tyr-Ser-Ile-A13-A14-Asp-A16-A17-A18-Gln-A20-A21-Phe-Val-A24-Trp-A26-Leu-A28-Gln-A30-A31-A32-A33-A34-A35-A36-A37-A38-A39-A40-P², or a pharmaceutically acceptable salt thereof;

wherein

P¹ represents a group represented by formula

-R^{A1},
-CO-R^{A1},
-CO-OR^{A1},
-CO-COR^{A1},
-SO-R^{A1},
-SO₂-R^{A1},
-SO₂-OR^{A1},
-CO-NR^{A2}R^{A3},
-SO₂-NR^{A2}R^{A3},
-C(=NR^{A1})-NR^{A2}R^{A3}, or

is absent,

wherein R^{A1}, R^{A2}, and R^{A3} each independently represent a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

P² represents -NH₂ or -OH;

A2: represents Aib, D-Ala, Ala, Gly, or Pro;

A9: represents Asp or Leu;

A13: represents Aib, or Ala;

A14: represents Leu, Aib, Lys;

A16: represents Arg, Ser, or Lys;

A17: represents Aib, Gln, or Ile;

A18: represents Ala, His, or Lys;

- A19: represents Gln, or Ala;
A20: represents Aib, Gln, Lys, or Ala;
A21: represents Asp, Asn, or Lys;
A24: represents Asn, or Glu;
A26: represents Leu or Lys;
A28: represents Ala, Lys, or Aib;
A29: represents Gln, Lys, Gly, or Aib;
A30: represents Arg, Gly, Ser, or Lys;
A31: represents Gly, Pro, or a deletion;
A32: represents Ser, Gly, or a deletion;
A33: represents Ser, Gly, or a deletion;
A34: represents Gly, Lys, Asn, or a deletion;
A35: represents Ala, Asp, Ser, Lys, or a deletion;
A36: represents Pro, Trp, Lys, or a deletion;
A37: represents Pro, Lys, Gly, or a deletion;
A38: represents Pro, His, Lys, or a deletion;
A39: represents Ser, Asn, Gly, Lys, or a deletion; and
A40: represents Ile, Lys or a deletion.

[Claim 2] The GIP receptor agonist peptide according to claim 1 or the pharmaceutically acceptable salt thereof, wherein A31 is Gly, A32-A39 are deletion; or A32 is Gly, A33-A39 are deletion.

[Claim 3] The GIP receptor agonist peptide according to claim 1 or the pharmaceutically acceptable salt thereof, wherein A31 is Pro and A32 is Gly, and A33-A39 are deletion.

[Claim 4] The GIP receptor agonist peptide according to any one of claims 1-3 or the pharmaceutically acceptable salt thereof, wherein P² is OH.

[Claim 5] A GIP receptor agonist peptide represented by formula (II):

P¹-Tyr-A2-Glu-Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-A13-A14-Asp-A16-A17-A18-A19-A20-A21-Phe-Val-A24-Trp-A26-Leu-Ala-A29-A30-A31-A32-A33-A34-A35-A36-A37-A38-A39-A40-P², or a pharmaceutically acceptable salt thereof, wherein:

P¹ represents a group represented by formula

-R^{A1},
-CO-R^{A1},
-CO-OR^{A1},
-CO-COR^{A1},
-SO-R^{A1},
-SO₂-R^{A1},
-SO₂-OR^{A1},
-CO-NR^{A2}R^{A3},
-SO₂-NR^{A2}R^{A3}, or
-C(=NR^{A1})-NR^{A2}R^{A3}

wherein R^{A1}, R^{A2}, and R^{A3} each independently represent a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;

P² represents -NH₂ or -OH;

A2: represents Aib, Ser, Ala, D-Ala, or Gly;

A13: represents Aib, Tyr, or Ala;

A14: represents Leu, or Lys(R);

A16: represents Arg, Ser, or Lys;

A17: represents Aib, Ile, Gln, or Lys(R);

A18: represents Ala, His, or Lys(R);

A19: represents Gln or Ala;

A20: represents Aib, Gln, or Lys(R);

A21: represents Asn, Glu, Asp, or Lys(R);

A24: represents Asn, or Glu;

A26: represents Leu or Lys(R);

A28: represents Ala, Aib, or Lys(R);

A29: represents Gln, Aib, or Lys(R);

A30: represents Arg, Gly, Lys, Ser, or Lys(R);

A31: represents Gly, Pro, or a deletion;

A32: represents Ser, Lys, Pro, Gly, or a deletion;

A33: represents Ser, Lys, Gly, or a deletion;

A34: represents Gly, Lys, Asn, or a deletion;

A35: represents Ala, Asp, Ser, Lys, or a deletion;

A36: represents Pro, Trp, Lys, or a deletion;

A37: represents Pro, Lys, Gly, or a deletion;

A38: represents Pro, His, Lys, or a deletion;

A39: represents Ser, Asn, Lys, Gly, or a deletion;

A40: represents Ile, Lys(R), or a deletion;

wherein in the residue Lys(R), the (R) portion represents X-L-, wherein L represents a linker, and is selected from the following group consisting of gE, GGGGG, GGEEE, G2E3, G3gEgE, 2OEGgEgE, OEGgEgE, GGPAPAP, 2OEGgE, 3OEGgEgE, G4gE, G5gE, 2OEGgEgEgE, 2OEG and G5gEgE; and X represents a lipid.

[Claim 6] A GIP receptor agonist peptide represented by formula (IV):

P¹-Tyr-A2-Glu-Gly-Thr-A6-A7-Ser-Asp-Tyr-Ser-Ile-A13-A14-Asp-A16-A17-A18-Gln-A20-A21-Phe-Val-Asn-Trp-Leu-Leu-A28-A29-A30-A31-A32-A33-A34-A35-A36-A37-A38-A39-P², or a pharmaceutically acceptable salt thereof;

wherein

P¹ represents H, C₁₋₆ alkyl, or absent;

P² represents -NH₂ or -OH;

A2 represents Aib, Gly, or Ser;

A6 represents Phe or Leu;

A7 represents Ile or Thr;

A13 represents Ala, Aib, or Tyr;

A14 represents Leu, Lys, or Lys(R);

A16 represents Lys, Arg, or Ser;

A17 represents Aib, Ile, Lys, or Lys(R);

A18 represents Ala, His, Lys, or Lys(R);

A20 represents Gln, Lys, Lys(R), or Aib;

A21 represents Asp, Lys, Lys(R), or Asn;

A28 represents Ala, Aib, or, Lys, Lys(R);

A29 represents Gln, Lys, Lys(R), or Aib;

A30 represents Lys, Ser, Arg, Lys(R), or Lys(Ac);

A31 represents Pro, Gly, or a deletion;

A32 represents Ser, Gly, or a deletion;

A33 represents Ser, Gly, or a deletion;

A34 represents Gly, Lys, or a deletion;

A35 represents Ala, Ser, Lys, or a deletion;

A36 represents Pro, Lys, or a deletion;

A37 represents Pro, Lys, Gly, or a deletion;

A38 represents Pro, Lys, or a deletion; and

A39 represents Ser, Gly, Lys, or a deletion,

wherein in the residue Lys(R), the (R) portion represents X-L-, wherein L represents a linker

and is selected from the group consisting of 1OEGgE, 2OEG, 2OEGgE, 2OEGgEgE,

2OEGgEgEgE, 3OEGgE, 3OEGgEgE, G2E3, G3gEgE, G4E2, G4gE, G4gEgE, GGGGG, G5E,

G5gE, G5gEgE, gE, gEgEgE, GGEEE, GGPAPAP, OEGgEgE, and OEGgEgEgE; and X

represents C₁₄-C₁₈ monoacid or C₁₄-C₁₈ diacid.

[Claim 7] The GIP receptor agonist peptide according to claim 6 or the pharmaceutically acceptable salt thereof, wherein

A14 represents Leu or Lys(R);

A17 represents Aib, Ile, or Lys(R);

A18 represents Ala, His, or Lys(R);

A20 represents Gln, Lys(R), or Aib;

A21 represents Asp, Lys(R), or Asn;

A28 represents Ala, Aib, or Lys(R);

A29 represents Gln, Lys(R), or Aib; and

A30 represents Lys, Ser, Arg, Lys(R), or Lys(Ac).

[Claim 8] The GIP receptor agonist peptide according to claim 6 or the pharmaceutically acceptable salt thereof, wherein

A2 represents Aib;

A17 represents Aib, Lys, or Lys(R);

A20 represents Aib; and

A28 represents Ala or Aib,

wherein L is selected from the group consisting of 2OEG, 2OEGgE, 2OEGgEgE, G2E3, G4gE, G4gEgE, G5, G5E, G5gE, G5gEgE, gEgEgE, GGEEE, GGPAPAP, OEGgEgE, and OEGgEgEgE.

[Claim 9] The GIP receptor agonist peptide according to claim 8 or the pharmaceutically acceptable salt thereof, wherein

A14 represents Leu or Lys(R);

A17 represents Aib or Lys(R).

A18 represents Ala, His, or Lys(R);

A21 represents Asp, Lys(R), or Asn;

A29 represents Gln, Lys(R), or Aib; and

A30 represents Lys, Ser, Arg, Lys(R), or Lys(Ac).

[Claim 10] The GIPR agonist peptide of any one of claims 5-9 or the pharmaceutically acceptable salt thereof, wherein the lipid X is C₁₄-C₁₆ monoacid or diacid.

[Claim 11] The GIPR agonist peptide of claim 10 or the pharmaceutically acceptable salt thereof, wherein the lipid X is a C₁₅ diacid or C₁₆ diacid.

[Claim 12] The GIPR agonist peptide of any one of claims 5-11 or the pharmaceutically acceptable salt thereof, wherein the linker L is 2OEGgEgE or GGGGG.

[Claim 13] The GIPR agonist peptide of any one of claims 5-12 or the pharmaceutically acceptable salt thereof, wherein (R) is 2OEGgEgE-C₁₅ diacid or 2OEGgEgE-C₁₆ diacid.

[Claim 14] The GIPR agonist peptide of any one of claims 5-13 or the pharmaceutically acceptable salt thereof, wherein the peptide has a Lys(R) amino acid residue at amino acid position A14 and (R) is 2OEGgEgE-C₁₆ diacid.

[Claim 15] The GIPR agonist peptide of any one of claims 5-13 or the pharmaceutically acceptable salt thereof, wherein the peptide has a Lys(R) amino acid residue at amino acid position A21 and (R) is 2OEGgEgE-C₁₅ diacid

[Claim 16] The GIPR agonist peptide of any one of claims 5-12 or the pharmaceutically acceptable salt thereof, represented by formula (V):

P¹-Tyr-Aib-Glu-Gly-The-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-A13-Leu-Asp-Arg-Aib-A18-Gln-Aib-A21-Phe-Val-Asn-Trp-Leu-Leu-Ala-Gln-A30-A31-A32-P², wherein

P¹ is methyl;

P² is OH or NH₂;

A13 represents Ala or Aib;

A18 represents Ala, Lys, or Lys(R);

A21 represents Lys, Lys(R), or Asp;

A30 represents Lys or Ser;

A31 represents Gly or Pro; and

A32 represents Gly or deletion;

wherein (R) represents X-L-, L represents 2OEGgEgE or GGGGG; and X represents a C₁₅ diacid or C₁₆ diacid.

[Claim 17] The GIPR agonist peptide of claim 16 or the pharmaceutically acceptable salt thereof, wherein

A18 represents Ala or Lys(R); and

A21 represents Lys(R) or Asp.

[Claim 18] The GIPR agonist peptide of any one of claims 5-13 and 16-17, or the pharmaceutically acceptable salt thereof, represented by the formula:

P¹-Y-Aib-E-G-T-F-I-S-D-Y-S-I-A-L-D-R-Aib-A-Q-Aib-Km-F-V-N-W-L-L-A-Q-K-G-P²;

wherein Km is Lys-2OEGgEgE-C₁₆ diacid,

P¹-Y-Aib-E-G-T-F-I-S-D-Y-S-I-Aib-L-D-R-Aib-Km-Q-Aib-D-F-V-N-W-L-L-A-Q-S-P-G-P²;

wherein Km is Lys-2OEGgEgE-C₁₆ diacid, or

P¹-Y-Aib-E-G-T-F-I-S-D-Y-S-I-A-L-D-R-Aib-A-Q-Aib-Km-F-V-N-W-L-L-A-Q-K-G-P²;

wherein Km is Lys-2OEGgEgE-C₁₅ diacid.

[Claim 19] The GIPR agonist peptide of any one of claims 16-18 or the pharmaceutically acceptable salt thereof, represented by the formula:

Me-Tyr-Aib-Glu-Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-Ala-Leu-Asp-Arg-Aib-Ala-Gln-Aib-

Lys(R)-Phe-Val-Asn-Trp-Leu-Leu-Ala-Gln-Lys-Gly-OH; wherein Lys(R) is Lys-2OEGgEgE-C₁₆ diacid.

[Claim 20] The GIPR agonist peptide of any one of claims 16-18 or the pharmaceutically acceptable salt thereof, represented by the formula:

Me-Tyr-Aib-Glu-Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-Asp-Arg-Aib-Lys(R)-Gln-Aib-Asp-Phe-Val-Asn-Trp-Leu-Leu-Ala-Gln-Ser-Pro-Gly-OH; wherein Lys(R) is Lys-2OEGgEgE-C₁₆ diacid.

[Claim 21] The GIPR agonist peptide of any one of claims 16-18 or the pharmaceutically acceptable salt thereof, represented by the formula:

Me-Tyr-Aib-Glu-Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-Ala-Leu-Asp-Arg-Aib-Ala-Gln-Aib-Lys(R)-Phe-Val-Asn-Trp-Leu-Leu-Ala-Gln-Lys-Gly-OH; wherein Lys(R) is Lys-2OEGgEgE-C₁₅ diacid.

[Claim 22] The GIP receptor agonist peptide according to any one of claims 5-7 or the pharmaceutically acceptable salt thereof, wherein the amino acid sequence comprises: Me-Tyr-Aib-Glu-Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-Ala-Leu-Asp-Arg-Aib-Ala-Gln-Aib-Lys(R)-Phe-Val-Asn-Trp-Leu-Leu-Ala-Gln-Arg-NH₂; wherein Lys(R) is Lys-2OEGgEgE-C₁₅ diacid.

[Claim 23] The GIP receptor agonist peptide according to any one of claims 5-9 or the pharmaceutically acceptable salt thereof, represented by:

Me-Tyr-Aib-Glu-Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-Aib-Lys(R)-Asp-Arg-Aib-Ala-Gln-Aib-Asn-Phe-Val-Asn-Trp-Leu-Leu-Ala-Gln-Ser-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-OH; wherein Lys(R) is Lys-GGGGG-C₁₅ diacid.

[Claim 24] The GIP receptor agonist peptide according to any one of claims 1-23 or a salt thereof, wherein the GIP receptor agonist peptide has a selectivity ratio, expressed as a ratio of (GLP1R EC₅₀ / GIPR EC₅₀) of greater than 10, or greater than 100, or greater than 1,000, or greater than 100,000.

[Claim 25] The GIP receptor agonist peptide according to any one of claims 1-23 or a salt thereof, wherein the GIP receptor agonist peptide has an IV T_{1/2} life of elimination of ranges between 4 – 10 hours.

[Claim 26] The GIP receptor agonist peptide according to claim 7 or 9, or a salt thereof, wherein the GIP receptor agonist peptide has a solubility of 15 mg/mL or greater.

[Claim 27] A medicament comprising the GIP receptor agonist peptide according to any one of claims 1-26, or a pharmaceutically acceptable salt thereof.

[Claim 28] A pharmaceutical composition comprising the GIP receptor agonist peptide according to any one of claims 1-26, or a pharmaceutically acceptable salt thereof.

[Claim 29] The GIP receptor agonist peptide according to any one of claims 1-26 or a salt thereof, or the medicament according to claim 27, or the pharmaceutical composition according to claim 28, which is administered to treat emesis as a monotherapy.

[Claim 30] The GIP receptor agonist peptide according to any one of claims 1-26 or a salt thereof, or the medicament according to claim 27, or the pharmaceutical composition according to claim 28, which is administered to a subject Q1D, or once per 24 hours to treat or prevent emesis, including vomiting and/or nausea.

[Claim 31] The medicament according to claim 27, which is an activator of a GIP receptor.

[Claim 32] The medicament according to claim 27, which is a suppressant for vomiting or nausea.

[Claim 33] Use of the GIP receptor agonist peptide of any one of claims 1-26, or a salt thereof, or the medicament according to claim 27, or the pharmaceutical composition according to claim 28, for the manufacture of a suppressant for vomiting or nausea.

[Claim 34] The GIP receptor agonist peptide of any one of claims 1-26 or a salt thereof, or the medicament according to claim 27, or the pharmaceutical composition according to claim 28, for use in suppressing vomiting or nausea.

[Claim 35] A method for preventing or treating emesis in a subject, comprising administering an effective amount of the peptide of any one of claims 1-26 or a salt thereof, or the medicament according to claim 27, or the pharmaceutical composition according to claim 28, to the subject.

[Claim 36] The method according to claim 35, wherein the emesis is nausea and/or vomiting.

[Claim 37] The medicament according to claim 32, the use according to claim 33, the peptide or a salt thereof, the medicament, or the pharmaceutical composition according to claim 34, or the method according to claim 36, where the emesis, vomiting or the nausea is caused by one or more conditions or causes selected from the following (1) to (10):

(1) Diseases accompanied by vomiting or nausea such as gastroparesis, gastrointestinal hypomotility, peritonitis, abdominal tumor, constipation, gastrointestinal obstruction, , chronic intestinal pseudo-obstruction, functional dyspepsia, cyclic vomiting syndrome, chronic unexplained nausea and vomiting, acute pancreatitis, chronic pancreatitis, hepatitis, hyperkalemia, cerebral edema, intracranial lesion, metabolic disorder, gastritis caused by an infection, postoperative disease, myocardial infarction, migraine, intracranial hypertension, and intracranial hypotension (e.g., altitude sickness);

(2) Vomiting and/or nausea induced by chemotherapeutic drugs such as (i) alkylating agents (e.g., cyclophosphamide, carmustine, lomustine, chlorambucil, streptozocin, dacarbazine, ifosfamide, temozolomide, busulfan, bendamustine, and melphalan), cytotoxic antibiotics (e.g., dactinomycin, doxorubicin, mitomycin-C, bleomycin, epirubicin, actinomycin D, amrubicin, idarubicin, daunorubicin, and pirarubicin), antimetabolic agents (e.g., cytarabine, methotrexate, 5-fluorouracil, enocitabine, and clofarabine), vinca alkaloids (e.g., etoposide, vinblastine, and vincristine), other chemotherapeutic agents such as cisplatin, procarbazine, hydroxyurea, azacytidine, irinotecan, interferon α , interleukin-2, oxaliplatin, carboplatin, nedaplatin, and miriplatin; (ii) opioid analgesics (e.g., morphine); (iii) dopamine receptor D1D2 agonists (e.g., apomorphine); (iv) cannabis and cannabinoid products including cannabis hyperemesis syndrome;

(3) Vomiting or nausea caused by radiation sickness or radiation therapy for the chest, the abdomen, or the like used to treat cancers;

(4) Vomiting or nausea caused by a poisonous substance or a toxin;

(5) Vomiting and nausea caused by pregnancy including hyperemesis gravidarium; and

(6) Vomiting and nausea caused by a vestibular disorder such as motion sickness or dizziness

(7) Opioid withdrawal;

(8) Pregnancy including hyperemesis gravidarium;

(9) A vestibular disorder such as motion sickness or dizziness; or

(10) A physical injury causing local, systemic, acute or chronic pain.

[Claim 38] The method according to claim 35, wherein the emesis is a result of cyclic vomiting syndrome or chemotherapy.

[Claim 39] The method of claim 35, wherein the subject is a non-type 2 diabetes mellitus subject.

[Claim 40] The method according to claim 35, wherein the emesis is delayed emesis or anticipatory emesis.

[Claim 41] The method according to any one of claims 35-40, wherein emesis is treated in the subject without inducing anxiety or sedation in the subject.

[Claim 42] The method according to any one of claims 35-41, wherein emesis is treated in the subject without inducing suppression of glucagon secretion when plasma glucose levels are above fasting levels.

[Claim 43] The method according to any one of claims 35-42, wherein emesis is treated in the subject without substantially activating the GLP-1 receptor.

[Claim 44] The method according to claim 42 or 43, wherein emesis is treated in the subject without concomitant, subsequent, or prior administration of a GLP-1 receptor agonist.

[Claim 45] The method according to any one of claims 35-44, wherein emesis is treated in a subject not taking a medicament to control a metabolic syndrome disorder.

[Claim 46] The method according to any one of claims 35-45, wherein emesis is treated in a subject taking a medicament to control a metabolic syndrome disorder.

[Claim 47] The method according to claim 46, wherein the metabolic syndrome disorder is type 2 diabetes mellitus or obesity.

[Claim 48] The method according to any one of claims 35-47, wherein the emesis is caused by or causes cyclic vomiting syndrome, or nausea or vomiting associated with chemotherapy.

[Claim 49] The method according to claim 38 or 48, wherein the chemotherapy or chemotherapeutic agent comprises: (i) alkylating agents (e.g., cyclophosphamide, carmustine, lomustine, chlorambucil, streptozocin, dacarbazine, ifosfamide, temozolomide, busulfan, bendamustine, and melphalan), cytotoxic antibiotics (e.g., dactinomycin, doxorubicin, mitomycin-C, bleomycin, epirubicin, actinomycin D, amrubicin, idarubicin, daunorubicin, and pirarubicin), antimetabolic agents (e.g., cytarabine, methotrexate, 5-fluorouracil, enocitabine, and clofarabine), vinca alkaloids (e.g., etoposide, vinblastine, and vincristine), other chemotherapeutic agents such as cisplatin, procarbazine, hydroxyurea, azacytidine, irinotecan, interferon α , interleukin-2, oxaliplatin, carboplatin, nedaplatin, and miriplatin; (ii) opioid analgesics (e.g., morphine); (iii) dopamine receptor D1D2 agonists (e.g., apomorphine); (iv) cannabis and cannabinoid products including cannabis hyperemesis syndrome

[Claim 50] The method according to claim 35, wherein the subject has type 2 diabetes mellitus.

[Claim 51] The method according to any one of claims 35-50, wherein the GIP receptor agonist peptide or medicament is administered subcutaneously, intravenously, intramuscularly, intraperitoneally, orally or via inhalation.

[Claim 52] The method according to any one of claims 35-51, wherein the effective amount of the GIP receptor agonist peptide administered to the subject is about 0.01 to 0.5 mg/kg/day, 0.1 to 5 mg/kg/day, 5 to 10 mg/kg/day, 10 to 20 mg/kg/day, 20 to 50 mg/kg/day, 10 to 100 mg/kg/day, 10 to 120 mg/kg/day, 50 to 100 mg/kg/day, 100 to 200 mg/kg/day, 200 to 300 mg/kg/day, 300 to 400 mg/kg/day, 400 to 500 mg/kg/day, 500 to 600 mg/kg/day, 600 to 700 mg/kg/day, 700 to 800 mg/kg/day, 800 to 900 mg/kg/day or 900 to 1000 mg/kg/day.

[Claim 53] The method according to any one of claims 35-52, wherein the subject is human.

[Claim 54] The method according to any one of claims 35-53, wherein the GIP receptor agonist peptide or medicament is administered to the subject before, during, or after the subject develops the disease-state.

[Claim 55] The method according to any one of claims 35-54, wherein the GIP receptor agonist peptide or medicament is administered to the subject 1 times per day, or 1 times per 24 hours.

[Claim 56] The method according to any one of claims 35-55, wherein the GIP receptor agonist peptide or medicament is administered to the subject for 1-5 days, 1-5 weeks, 1-5 months, or 1-5 years.