

METHODS AND USES FOR TREATING NAUSEA AND EMESIS

PRIORITY

[1] This application claims the benefit of, and claims priority to, U.S. Provisional Application No. 63/493,384, filed March 31, 2023, and U.S. Provisional Application No. 63/585,493, filed on September 26, 2023, the contents of which are hereby incorporated by reference in their entirety.

INCORPORATION BY REFERENCE OF A SEQUENCE LISTING

[2] A Sequence Listing is provided herewith as a Sequence Listing XML, "30286_WO" created on February 15, 2024, and having a size of 25 KB. The contents of the Sequence Listing XML are incorporated by reference herein in their entirety.

FIELD

[3] The present disclosure relates to compositions, particularly, long-acting peptide compounds having activity at the human glucose-dependent insulinotropic polypeptide receptor (GIP-R) and methods of use for treating and preventing nausea and emesis in a patient, or a symptom or condition associated with nausea and emesis.

BACKGROUND

[4] Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are two of the primary incretin peptide hormones secreted from the intestine on ingestion of glucose or nutrients to stimulate insulin secretion from pancreatic β -cells. GIP and GLP-1 exert their effects by binding to their specific receptors, the GIP receptor (GIP-R) and the GLP-1 receptor (GLP-1R), which belong to the G-protein coupled receptor family. While GIP is the primary incretin peptide hormone for improving glycemic control, other therapies which focus on GLP-1 receptor agonism (*e.g.*, liraglutide, semaglutide, and dulaglutide) are effective at managing glucose control as well as reducing weight, making them an ideal therapeutic for treating Type 2 diabetes mellitus or obesity. However, a major concern is that these GLP-1 receptor peptide agonists may be associated with adverse side effects, *e.g.*, nausea and emesis.

[5] Similarly, nausea and vomiting are common adverse side effects in patients receiving chemotherapy for the treatment for cancer. These include administration of high and moderate emetic risk chemotherapies, which result in chemotherapy-induced nausea and

vomiting (CINV). The need for new therapies to prevent and treat nausea and emesis in patients is of high priority, especially in patients receiving therapies for Type 2 diabetes mellitus, obesity, and cancer. In the various aspects and embodiments of this disclosure compositions and methods for preventing and treating nausea and emesis are provided.

SUMMARY

[6] In some embodiments, the present disclosure provides a method for treating or preventing nausea or emesis in a patient, the method comprising administering a therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.

[7] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is about 0.3 mg to 30 mg.

[8] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is about 5 mg to 30 mg.

[9] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is 7.5 mg.

[10] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is 20 mg.

[11] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is 25 mg.

[12] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is formulated into a medicament.

[13] In some embodiments, the treatment of nausea or emesis is in the patient taking a medicament to treat a metabolic syndrome disorder.

[14] In some embodiments, the metabolic syndrome disorder is Type 2 diabetes mellitus or obesity.

[15] In some embodiments, the medicament to treat the metabolic syndrome disorder is selected from the group consisting of a GLP-1 receptor agonist peptide, a dual agonist peptide of the GLP-1 and glucagon (GCG) receptors, a long-acting-agonist peptide of the amylin receptor, a dual amylin and calcitonin receptor agonist peptide, a monoclonal antibody directed to the leptin receptor, a urocortin peptide, or a peptide tyrosine-tyrosine (PYY) analog to the patient.

[16] In some embodiments, the medicament to treat the metabolic syndrome disorder is selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9, or a pharmaceutically acceptable salt thereof.

[17] In some embodiments, the patient's tolerance to nausea or emesis-inducing treatment of the metabolic syndrome disorder is improved.

[18] In some embodiments, the medicament to treat the metabolic syndrome disorder is administered without titration.

[19] In some embodiments, the treatment of nausea or emesis is in the patient taking a chemotherapeutic agent.

[20] In some embodiments, the chemotherapeutic agent is selected from the group consisting of anthracycline, cyclophosphamide, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, epirubicin, fam-trastuzumab deruxtecan-nxki, ifosfamide, mechlorethamine, melphalan, sacituzumab govitecan-hzly, and streptozocin.

[21] In some embodiments, the chemotherapeutic agent is selected from the group consisting of aldesleukin, amifostine, bendamustine, busulfan, carboplatin, carmustine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, dinutuximab, doxorubicin, dual-drug liposomal encapsulation of cytarabine and daunorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, irinotecan (liposomal), lurbinectedin, melphalan, methotrexate, mirvetuximab soratansine-gynx, naxitamab-gqgk, oxaliplatin, romidepsin, temozolomide, and trabectedin.

[22] In some embodiments, the chemotherapeutic agent is cisplatin.

[23] In some embodiments, the chemotherapeutic agent is a combination of cyclophosphamide and an anthracycline.

[24] In some embodiments, the anthracycline is selected from the group consisting of doxorubicin, daunorubicin, and idarubicin.

[25] In some embodiments, the patient's tolerance to the nausea or emesis inducing treatment with the chemotherapeutic agent is improved.

[26] In some embodiments, the chemotherapeutic agent is administered without titration.

[27] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered subcutaneously, intravenously, intramuscularly, intraperitoneally, orally, or via inhalation.

[28] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered to the patient one time, once weekly, twice monthly, once every three weeks, once monthly, or once yearly.

[29] In some embodiments, the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered subcutaneously to the patient once weekly.

[30] In some embodiments, use of a pharmaceutical composition comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for treating or preventing nausea or emesis in a patient.

[31] In some embodiments, use of the compound of comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of nausea or emesis in a patient.

[32] In some embodiments, a pharmaceutical composition comprising the compound of SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for use in treating or preventing nausea or emesis in a patient.

DETAILED DESCRIPTION

[33] In various aspects and embodiments, the present disclosure provides compositions and methods for treating or preventing nausea or emesis. In accordance with aspects of the disclosure, the compositions comprise long-acting GIP receptor agonist peptides that target GIP-R. In some embodiments, the long-acting GIP receptor agonist peptides comprise SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutical acceptable salt thereof. In some embodiments, the long-acting GIP receptor agonist peptides comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutical acceptable salt thereof, are effective in treating nausea or emesis.

[34] Furthermore, the present disclosure also provides for methods to clinically manage (e.g. treat, prevent and/or reduce the incidence of) nausea or emesis resulting from the administration of therapeutics that cause nausea and emesis (e.g., GLP-1 receptor agonist peptides and chemotherapeutic drugs). The compositions and methods disclosed herein comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, have been shown to treat, prevent and/or reduce the incidence of negative side effects of nausea and emesis and improve the tolerability of nausea-inducing therapies. Improved tolerability of the nausea-inducing therapies in a patient disclosed herein, particularly in the Examples, and is measured by tallying the number of emetic episodes in a patient who is receiving a long-acting GIP receptor agonist peptide, e.g., SEQ ID NO:1 or SEQ ID NO:2, with treatment for cancer (e.g., chemotherapy), or treatment for Type 2 diabetes mellitus or obesity (e.g., a GLP-1 agonist peptide), and is characterized by strong rhythmic abdominal contractions associated with either oral expulsion from the gastrointestinal tract (i.e., vomiting) or without the passage of materials (i.e., retching).

[35] In some embodiments, the present disclosure provides a method for treating or preventing nausea or emesis in a patient, the method comprising administering a therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.

[36] In one embodiment, the present disclosure provides a GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, for use in treating or preventing nausea or emesis. In another embodiment, the present disclosure provides a GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for use in treating or preventing nausea or emesis.

[37] In one embodiment, the present disclosure provides a GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, for use in treating nausea or emesis, wherein the GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of about 0.3 mg to 30 mg. In another embodiment, the present disclosure provides a GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for use in treating nausea or emesis, wherein the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of about 0.3 mg to 30 mg.

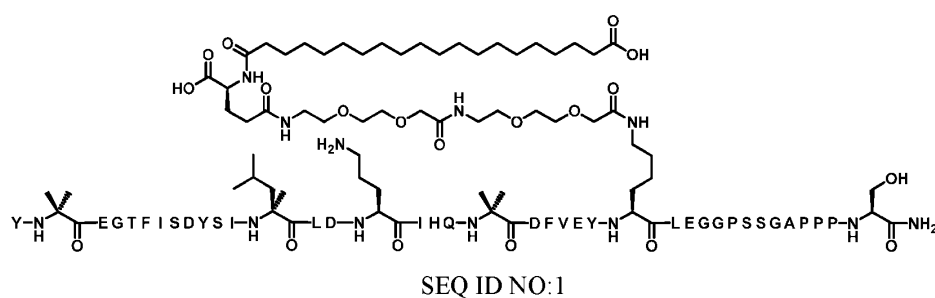
[38] In one embodiment, the present disclosure provides a GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, for use in treating nausea or emesis, wherein the compound comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered once weekly at a dose of about 0.3 mg to 30 mg. In another embodiment, the present disclosure provides a GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for use in treating nausea or emesis, wherein the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered once weekly at a dose of about 0.3 mg to 30 mg.

[39] In one embodiment, the present disclosure provides use of a pharmaceutical composition comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for treating or preventing nausea or emesis in a patient.

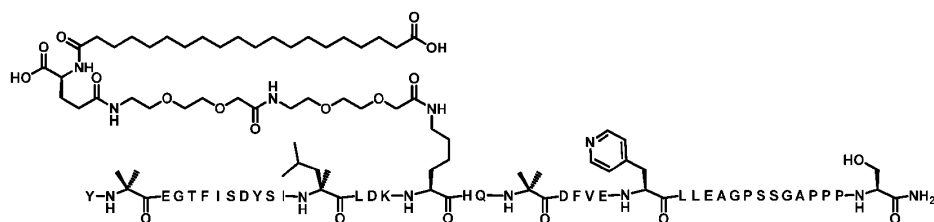
[40] In some embodiments, the present disclosure provides use of the compound of comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of nausea or emesis in a patient.

[41] In some embodiments, the present disclosure provides a pharmaceutical composition comprising the compound of SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for use in treating or preventing nausea or emesis in a patient.

[42] In some embodiments described herein, the GIP receptor agonist peptide comprises SEQ ID NO:1. The chemical structure of SEQ ID NO:1 is described using the standard single letter amino acid codes, except for residues Aib2, αMeL13, Orn16, Aib20, K26, and Ser39, wherein the structures of the amino acid residues have been expanded:



[43] The chemical structure of SEQ ID NO:2 is described using the standard single letter amino acids with the exception of residues Aib2, αMeL13, K17, Aib20, 4-Pal25, and Ser39, wherein the structures of these amino acid residues have been expanded:



SEO ID NO:2

[44] In some embodiments, a therapeutically effective amount of a GIP receptor agonist peptide to prevent or treat nausea or emesis in a patient in need thereof may range from about 0.3 to 30 mg, or about 5.0 to 50 mg.

[45] In some embodiments, the present disclosure provides a method for treating or preventing nausea or emesis in a patient in need thereof, comprising administering a therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1 is about 0.3 mg to 30 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1 is 7.5 mg. In other embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1 is 20 mg. In other embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1 is 25 mg.

[46] In some embodiments, the present disclosure provides a method for treating or preventing nausea or emesis in a patient in need thereof, comprising administering a therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:2 or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:2 is about 0.3 mg to 30 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:2 is 7.5 mg. In other embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:2 is 20 mg. In other embodiments, the therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:2 is 25 mg.

[47] In some embodiments, the present disclosure provides a method of treating or preventing nausea or emesis in a patient in need thereof, comprising administering a therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:1 or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:1 is about 0.3 mg to 30 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:1 is 7.5 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO: 1 is 25 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:1 is 25 mg.

[48] In some embodiments, the present disclosure provides a method of treating or preventing nausea or emesis in a patient in need thereof, comprising administering a therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:2 or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:2 is about 0.3 mg to 30 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:2 is 7.5 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO: 2 is 20 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting of SEQ ID NO:2 is 25 mg.

[49] In some embodiments, the present disclosure provides a method of treating or preventing nausea or emesis in a patient in need thereof, comprising administering a therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:1 is about 0.3 mg to 30 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:1 is 7.5 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:1 is 20 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:1 is 25 mg.

[50] In some embodiments, the present disclosure provides a method of treating or preventing nausea or emesis in a patient in need thereof, comprising administering a

therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:2, or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:2 is about 0.3 mg to 30 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:2 is 7.5 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:2 is 20 mg. In some embodiments, the therapeutically effective amount of a GIP receptor agonist peptide consisting essentially of SEQ ID NO:2 is 25 mg.

[51] In some embodiments, the GIP receptor agonist peptide of the present disclosure comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is formulated into a medicament.

[52] In some embodiments, the GIP receptor agonist peptide of the present disclosure comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy to treat or prevent nausea or emesis in a patient. In some instances, the GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2, can be administered, for example, every week, twice per week, every other week, every 3 weeks, every month, every 2 months, every 3 months, every 4 months, every 5 months or every 6 months. In some embodiments, the GIP receptor agonist peptide of the present disclosure can be administered to the patient once per week, for 1-5 weeks, 1-5 months, or 1-5 years. In some embodiments, the GIP receptor agonist peptide of the present disclosure comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered to treat nausea or emesis in a patient without concomitant, subsequent, or prior administration of a GLP-1 receptor agonist.

[53] In some embodiments, the GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2, can be administered to a patient in need thereof, for example, in combination with another drug that does not adversely influence the GIP receptor agonist peptide of the present disclosure, for the purpose of, for example, promoting the action (antiemetic action) of the GIP receptor agonist peptide of the present disclosure, reducing the dose of the GIP receptor agonist peptide of the present disclosure, and the like.

[54] In some embodiments, the patient in need thereof is administered a GIP receptor agonist peptide with a concomitant dose of another drug used to treat a metabolic syndrome disorder. In other embodiments herein, the patient in need thereof is administered a GIP

receptor agonist peptide with a subsequent dose of another drug used to treat a metabolic syndrome disorder. In still another embodiment herein, the the patient in need thereof is administered a GIP receptor agonist peptide with a prior dose of another drug used to treat a metabolic syndrome disorder. In another embodiment herein, the patient in need thereof is administered a sequential, simultaneous, or separate combination of a GIP receptor agonist with another drug used to treat a metabolic syndrome disorder.

[55] In some embodiments, the metabolic syndrome disorder is Type 2 diabetes mellitus or obesity.

[56] Examples of therapeutic agents that can be further administered a second therapeutic agent in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2, (hereinafter sometimes to be abbreviated as a concomitant drug), and includes anti-obesity agents, therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agents for hyperlipidemia, antihypertensive agents, diuretics, and chemotherapeutics.

[57] In some embodiments, the GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2, is administered prior to administration of an anti-obesity agent, therapeutic agent for diabetes, therapeutic agent for diabetic complications, therapeutic agent for hyperlipidemia, antihypertensive agent, a diuretic, and a chemotherapy.

[58] In some embodiments of the present disclosure, a patient in need thereof is further administered a second therapeutic agent selected from the group consisting of a GLP-1 receptor agonist peptide (SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5) a dual agonist peptide of the GLP-1 and glucagon (GCG) receptors (SEQ ID NO:6), a long-acting-agonist peptide of the amylin receptor (SEQ ID NO:7), a dual amylin and calcitonin receptor agonist peptide (SEQ ID NO:8), a monoclonal antibody directed to the leptin receptor, a urocortin peptide, or a peptide tyrosine-tyrosine (PYY) analog (SEQ ID NO:9).

[59] In some embodiments of the present disclosure, a patient in need thereof is further administered a second therapeutic agent selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9, or a pharmaceutically acceptable salt thereof.

[60] In some embodiments, a GLP-1 receptor agonist peptide comprising SEQ ID NO:3 is administered in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, the patient in need thereof is administered a sequential, simultaneous, or separate therapeutic regimen of SEQ ID NO:3 in

combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2 for the treatment of nausea or emesis. In some embodiments, a GLP-1 receptor agonist peptide comprising SEQ ID NO:4 is administered in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, the patient in need thereof is administered a sequential, simultaneous, or separate therapeutic regimen of SEQ ID NO:4 in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2 for the treatment of nausea or emesis. In some embodiments, a GLP-1 receptor agonist peptide comprising SEQ ID NO:5 is administered in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, the patient in need thereof is administered a sequential, simultaneous, or separate therapeutic regimen of SEQ ID NO:5 in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2 for the treatment of nausea or emesis. In some embodiments, a dual agonist peptide of the GLP-1 and glucagon (GCG) receptors comprising SEQ ID NO:6 is administered in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, the patient in need thereof is administered a sequential, simultaneous, or separate therapeutic regimen of SEQ ID NO:6 in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2 for the treatment of nausea or emesis. In some embodiments, a long-acting-agonist peptide of the amylin receptor comprising SEQ ID NO:7 is administered in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, the patient in need thereof is administered a sequential, simultaneous, or separate therapeutic regimen of SEQ ID NO:7 in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2 for the treatment of nausea or emesis. In some embodiments, a dual amylin and calcitonin receptor agonist peptide comprising SEQ ID NO:8 is administered in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, the patient in need thereof is administered a sequential, simultaneous, or separate therapeutic regimen of SEQ ID NO:8 in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2 for the treatment of nausea or emesis. In some embodiments, a peptide tyrosine-tyrosine (PYY) analog comprising SEQ ID NO:9 is administered in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2. In some

embodiments, the patient in need thereof is administered a sequential, simultaneous, or separate therapeutic regimen of SEQ ID NO:9 in combination with a GIP receptor agonist peptide of the present disclosure, e.g., SEQ ID NO:1 or SEQ ID NO:2 for the treatment of nausea or emesis.

[61] In some embodiments of the present disclosure, a patient in need thereof is further administered a second therapeutic agent, wherein the second therapeutic agent is a chemotherapeutic agent.

[62] In some embodiments of the present disclosure, the chemotherapeutic agent is selected from the group consisting of altretamine, bendamustine, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, mechlorethamine, melphalan, oxaliplatin, procarbazine, temozolomide, thiotepa, trabectedin, carmustine, lomustine, streptozocin, 5-fluorouracil, 6-mercaptopurine, azacytidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, gemcitabine, hydroxyurea, methotrexate, nelarabine, pemetrexed, pentostatin, pralatrexate, thioguanine, trifluridine/tipiracil combination, etoposide, irinotecan, irinotecan liposomal, mitoxantrone, teniposide, topotecan, cabazitaxel, docetaxel, nab-paclitaxel, paclitaxel, vinblastine, vincristine, vincristine liposomal, vinorelbine, daunorubicin, doxorubicin, doxorubicin liposomal, epirubicin, idarubicin, mitoxantrone, valrubicin, bleomycin, dactinomycin, mitomycin-C, all-trans-retinoic acid, arsenic trioxide, asparaginase, eribulin, ixabepilone, mitotane, omacetaxine, pegaspargase, procarbazine, romidepsin, vorinostat, or any combinations thereof.

[63] In some embodiments, the chemotherapeutic agent is a chemotherapeutic agent with a high emetic risk (e.g., >90% frequency of emesis) selected from the group consisting of anthracycline, cyclophosphamide, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, epirubicin, fam-trastuzumab deruxtecan-nxki, ifosfamide, mechlorethamine, melphalan, sacituzumab govitecan-hzly, and streptozocin.

[64] In some other embodiments, the chemotherapeutic agent is a chemotherapeutic agent with moderate emetic risk (e.g., >30%-90% frequency of emesis) selected from the group consisting of aldesleukin, amifostine, bendamustine, busulfan, carboplatin, carmustine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, dinutuximab, doxorubicin, dual-drug liposomal encapsulation of cytarabine and daunorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, irinotecan (liposomal), lurbectedin, melphalan,

methotrexate, mirvetuximab soratansine-gynx, naxitamab-gqgk, oxaliplatin, romidepsin, temozolomide, and trabectedin.

[65] In some embodiments, the chemotherapeutic agent is cisplatin.

[66] In some other embodiments, the chemotherapeutic agent is a combination of cyclophosphamide and an anthracycline.

[67] In some embodiments, the anthracycline is selected from the group consisting of doxorubicin, daunorubicin, and idarubicin.

[68] In some embodiments, the patient is administered a sequential, simultaneous, or separate therapeutic regimen of a GIP receptor agonist peptide in combination with a chemotherapeutic agent for the treatment of nausea or emesis.

[69] In some embodiments, the present disclosure provides a method wherein the patient's tolerance to treatment with a second therapeutic agent is improved. In another embodiment, the patient's tolerance to treatment with a chemotherapeutic agent is improved. In yet another embodiment, the present disclosure provides a method wherein the patient's tolerance to treatment with a second therapeutic agent administered to treat a metabolic syndrome disorder is improved. In an embodiment, the present disclosure provides a method wherein the patient's tolerance to treatment with a second therapeutic agent is selected from the group consisting of selected from the group consisting of a GLP-1 receptor agonist peptide (SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5) a dual agonist peptide of the GLP-1 and glucagon (GCG) receptors (SEQ ID NO:6), a long-acting-agonist peptide of the amylin receptor (SEQ ID NO:7), a dual amylin and calcitonin receptor agonist peptide (SEQ ID NO:8), a monoclonal antibody directed to the leptin receptor, a urocortin peptide, or a peptide tyrosine-tyrosine (PYY) analog (SEQ ID NO:9).

[70] In an embodiment, the present disclosure provides a method wherein the second therapeutic agent is administered without titration. In an embodiment, the present disclosure provides a method wherein the chemotherapeutic agent is administered without titration. In an embodiment, the present disclosure provides a method wherein the second therapeutic agent is administered to treat a metabolic syndrome disorder is administered without titration. In an embodiment, the present disclosure provides a method wherein the second therapeutic agent is selected from the group consisting of a a GLP-1 receptor agonist peptide (SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5) a dual agonist peptide of the GLP-1 and glucagon (GCG) receptors (SEQ ID NO:6), a long-acting-agonist peptide of the amylin receptor (SEQ ID NO:7), a dual amylin and calcitonin receptor agonist peptide (SEQ ID NO:8), a

monoclonal antibody directed to the leptin receptor, a urocortin peptide, or a peptide tyrosine-tyrosine (PYY) analog (SEQ ID NO:9), is administered without titration.

[71] In a more specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of 7.5 mg. In a more specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of 7.5 mg.

[72] In a more specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of 20 mg. In a more specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of 20 mg.

[73] In a more specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of 25 mg. In a more specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered in at least one dose of 25 mg.

[74] In another specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered in a once weekly dose of 7.5 mg. In another specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered in a once weekly dose of 7.5 mg.

[75] In another specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered in a once weekly dose of 20 mg.

[76] In another specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered in a once weekly dose of 20 mg.

[77] In another specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered in a once weekly dose of 25 mg.

[78] In another specific embodiment, the GIP receptor agonist peptide comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered in a once weekly dose of 25 mg.

[79] In an embodiment, the present disclosure provides a use of a GIP receptor agonist peptide comprising SEQ ID NO:1 in the manufacture of a medicament for the treatment of nausea or emesis. In another embodiment, the present disclosure provides a use of a GIP receptor agonist peptide comprising SEQ ID NO:1 in the manufacture of a medicament for the treatment of nausea only. In another embodiment, the present disclosure provides a use of a GIP receptor agonist peptide comprising SEQ ID NO:1 in the manufacture of a medicament for the treatment of emesis only.

[80] In an embodiment, the present disclosure provides a use of a GIP receptor agonist peptide comprising SEQ ID NO:2 in the manufacture of a medicament for the treatment of nausea or emesis. In another embodiment, the present disclosure provides a use of a GIP receptor agonist peptide comprising SEQ ID NO:2 in the manufacture of a medicament for the treatment of nausea only. In an embodiment, the present disclosure provides a use of a GIP receptor agonist peptide comprising SEQ ID NO:2 in the manufacture of a medicament for the treatment of emesis only.

[81] In some embodiments disclosed herein, the nausea or emesis is acute. In other embodiments disclosed herein, the nausea or emesis is chronic. In yet other embodiments disclosed herein, the nausea or emesis is anticipatory.

[82] In the embodiments disclosed herein, the GIP receptor agonist peptide, e.g., SEQ ID NO:1 or SEQ ID NO:2, is administered one time. In other embodiments disclosed herein, the GIP receptor agonist peptide is administered once weekly. In other embodiments disclosed herein, the the GIP receptor agonist peptide is administered twice monthly. In other embodiments disclosed herein, the GIP receptor agonist peptide is administered once every three weeks. In other embodiments disclosed herein, the GIP receptor agonist peptide is administered once monthly. In other embodiments disclosed herein, the GIP receptor agonist peptide is administered once yearly.

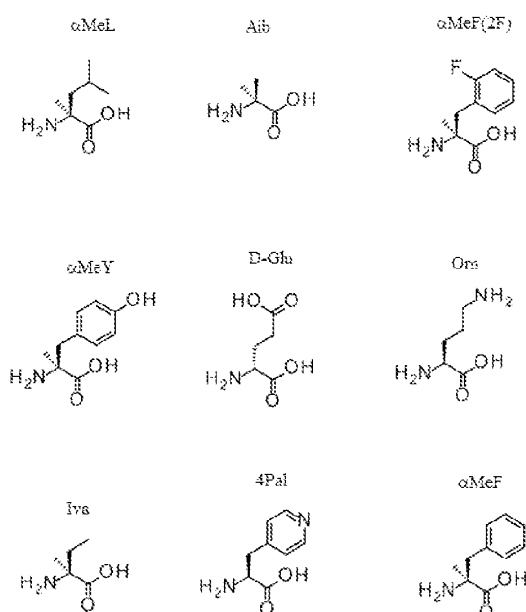
[83] In the embodiments disclosed herein, the therapeutically effective amount of the GIP receptor agonist peptide, e.g., SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered subcutaneously to the patient once weekly.

[84] In certain embodiments disclosed herein, the patient in need thereof is affected by one or more conditions selected from the group consisting of: (1) pregnancy; (2) cyclic vomiting syndrome; (3) infection; (4) ingestion of poisonous substances; (5) motion sickness; and (6) chemotherapy-induced nausea and vomiting (CINV). In a specific embodiment herein, the nausea or emesis is caused by hyperemesis gravidarum of pregnancy.

[85] Reference to an element by the indefinite article “a” or “an” does not exclude the possibility that more than one element is present, unless the context clearly requires that there be one and only one element. The indefinite article “a” or “an” thus usually means “at least one.”

[86] As disclosed herein, “administration” means the practice of providing a patient with a substance intended for the diagnosis, treatment, or prevention of a medical illness or condition. As used herein, the administration of GIP receptor agonist peptides comprising SEQ ID NO:1 or SEQ ID NO:2 may be administered concomitantly, prior to, or subsequently to, a second therapeutic agent. The timing of administration can also be concomitantly to, prior to, or subsequently to the onset of nausea or emesis.

[87] As disclosed herein, the term “amino acid” means both naturally occurring amino acids and unnatural amino acids. The amino acids are typically depicted using standard one letter codes (e.g., L=leucine), as well as alpha-methyl substituted residues of natural amino acids (e.g., α -methyl leucine, or α MeL, and α -methyl phenylalanine, or α MeF) and certain other unnatural amino acids, such as alpha-amino isobutyric acid, or “Aib”, “4-Pal”, “Orn”, and the like. The structures of these amino acids appear below:



[88] As disclosed herein, “Orn” means L-ornithine. As disclosed herein, “4Pal” means 3-(4-Pyridyl)-L- alanine. As disclosed herein, “αMeF(2F)” means alpha-methyl 2-fluoro-L-phenylalanine. As disclosed herein, “αMeY” and “αMeL” mean alpha-methyl-L-tyrosine and alpha-methyl-L- leucine, respectively. As disclosed herein, “e” and “D-Glu” mean D-glutamic acid. As disclosed herein, “D-Tyr” and “y” each mean D-tyrosine. As disclosed herein, “D-Ala” and “a” each mean D-alanine. As disclosed herein, “αMeF” means alpha-methyl-F and alpha-methyl-Phe. As disclosed herein “Iva” means L-isovaline.

[89] The term “chemotherapeutic agent” as disclosed herein refers to a medication that is used to treat cancer by killing or preventing the growth of malignant cells.

[90] Chemotherapeutic agents are toxic to cells with high proliferative rates and may cause side effects like nausea and vomiting. Doctors classify chemotherapy drugs according to their emetogenic potential (i.e., how likely the drug will cause nausea or vomiting) as high emetic risk, moderate emetic risk, low emetic risk, or minimal emetic risk.

[91] Non-limiting examples of chemotherapeutic agents include altretamine, bendamustine, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, mechlorethamine, melphalan, oxaliplatin, procarbazine, temozolomide, thiotepta, trabectedin, carmustine, lomustine, streptozocin, 5-fluorouracil, 6mercaptapurine, azacytidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine,

floxuridine, fludarabine, gemcitabine, hydroxyurea, methotrexate, nelarabine, pemetrexed, pentostatin, pralatrexate, thioguanine, trifluridine/tipiricail combination, etoposide, irinotecan, irinotecan liposomal, mitoxantrone, teniposide, topotecan, cabazitaxel, docetaxel, nab-paclitaxel, paclitaxel, vinblastine, vincristine, vincristine liposomal, vinorelbine, daunorubicin, doxorubicin, doxorubicin liposomal, epirubicin, idarubicin, mitoxantrone, valrubicin, bleomycin, dactinomycin, mitomycin-C, all-trans-retinoic acid, arsenic trioxide, asparaginase, eribulin, ixabepilone, mitotane, omacetaxine, pegaspargase, procarbazine, romidepsin, vorinostat, or any combinations thereof.

[92] Non-limiting examples of chemotherapeutic agents with high emetic risk (>90% frequency of emesis) are anthracycline, cyclophosphamide, carboplatin, carmustine (>250 mg/m²), cisplatin, cyclophosphamide (> 1500 mg/m²), dacarbazine, doxorubicin (≥60 mg/m²), epirubicin (>90 mg/m²) fam-trastuzumab deruxtecan-nxki, ifosfamide (≥2 g/m² per dose), mechlorethamine, melphalan (≥140 mg/m²), sacituzumab govitecan-hzly, streptozocin, or any combinations thereof.

[93] Non-limiting examples of chemotherapeutic agents with moderate emetic risk (>30%-90% frequency of emesis) are aldesleukin (>12-15 million IU/m²), amifostine (>300 mg/m²), bendamustine, busulfan, carboplatin (AUC< 4), carmustine (<250 mg/m²), clofarabine, cyclophosphamide (<1500 mg/m²), cytarabine (>200 mg/m²), dactinomycin, daunorubicin, dinutuximab, doxorubicin, dual-drug liposomal encapsulation of cytarabine and daunorubicin, epirubicin (≤90 mg/m²), idarubicin, ifosfamide (<2 g/m² per dose), irinotecan, irinotecan (liposomal), lurbectedin, melphalan (<140 mg/m²), methotrexate (≥250 mg/m²), mirvetuximab soratansine-gynx, naxitamab-gqgk, oxaliplatin, romidepsin, temozolomide, trabectedin, or any combinations thereof.

[94] The term “chemotherapy-induced nausea and vomiting” or “CINV” refers to a side effect of cancer treatment. CINV may be classified as acute, anticipatory, breakthrough, delayed, or refractory.

[95] The term “cyclic vomiting syndrome” as disclosed herein refers to a syndrome characterized by episodes of severe vomiting that have no apparent cause. Episodes of cyclic vomiting can last for hours or days and may alternate with symptom-free periods.

[96] The term “dose” as disclosed herein refers to an amount (e.g., a concentration) of a medicament taken or recommended to be taken.

[97] The term “emesis” or “emetic episodes” as disclosed herein refers to strong rhythmic abdominal contractions associated with either oral expulsion from the gastrointestinal tract

(i.e., vomiting) or without the passage of materials (i.e. retching). Emesis may be caused by a medication, such as chemotherapy, e.g., cisplatin. In some embodiments, nausea and vomiting may be caused by an underlying condition, such as hyperemesis gravidarum of pregnancy, cyclic vomiting syndrome, or an infection. In some embodiments, nausea and vomiting may be caused by opioid analgesics, the ingestion of poisonous substances, motion sickness, or concomitant treatment with medications inducing or having the potential to induce nausea or vomiting, such as medications used to treat metabolic syndromes.

[98] As disclosed herein, “fatty acid” consists of a straight chain of an even number of carbon atoms, with hydrogen atoms along the length of the chain and at one end (monoacid) or both ends (diacid) of the chain a carboxyl group (-COOH). In a preferred embodiment, the “fatty acid” moiety is a C₂₀ diacid.

[99] As disclosed herein, “hyperemesis gravidarum” refers to the most severe form of nausea and vomiting during pregnancy. Hyperemesis gravidarum is a condition characterized by severe nausea, vomiting, weight loss, and electrolyte disturbance.

[100] As disclosed herein, “long-acting” means that binding affinity and activity of a composition described herein continues for a period of time greater than native peptide or protein. Dosing and administration schedules can vary, depending on the condition of the patient, and the chemistry of the long acting GIP agonist peptides, e.g., SEQ ID NO:1 and SEQ ID NO:2. In various embodiments, the long-acting GIP agonist peptides are administered about weekly, about bi-monthly (i.e., about every other week), about monthly, or about quarterly, or yearly. Dosing and administration schedules can further include varying dosing and administration frequency based on the patient’s response.

[101] As disclosed herein, “metabolic syndrome disorder” refers to any of a cluster of conditions that often occur together and increase a person’s risk of heart disease, stroke, and type 2 diabetes mellitus. These conditions may include high blood sugar, high blood pressure, low levels of HDL cholesterol, high levels of triglycerides in the blood, and a large waist circumference. Non-limiting examples of drugs used to treat metabolic syndromes include GLP-1 receptor agonist peptides, such as liraglutide, semaglutide, or dulaglutide; dual agonists of the GLP-1 and GCG receptors; amylin receptor agonist peptides; dual agonists of both the amylin and calcitonin receptors; monoclonal antibodies directed to the leptin receptor; peptide tyrosine-tyrosine (PYY) analogs; or urocortin peptides.

[102] As disclosed herein, “motion sickness” refers to a feeling of sickness induced by motion. Motion sickness refers to, for example, repeated movements when travelling, like going over bumps in a car or rocking in a boat.

[103] As disclosed herein, the term “nausea” refers to the unpleasant sensation of having the urge to vomit. Nausea is a subjective unpleasant feeling in the back of one's throat and stomach that may lead to vomiting. There are many words that describe nausea including, but not limited to, sick to my stomach, queasy, or upset stomach. Nausea can have other symptoms that happen at the same time, such as increased saliva (spit), dizziness, light-headedness, trouble swallowing, skin temperature changes, and a fast heart rate.

[104] The term “patient” as disclosed herein refers to a human or an animal. In a preferred embodiment, the patient is a human. In a certain embodiment, the patient is further characterized with having nausea or emesis, or at risk for acquiring nausea or emesis. In further embodiments, said patient would benefit from the therapeutic effects of long-acting GIP agonism which would treat or prevent said nausea or emesis.

[105] By “reduce” or “inhibit” the terms refer to the ability to cause an overall decrease of 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or greater. In some embodiments, reduce or inhibit can refer to a relative reduction compared to a reference (e.g., reference level of biological activity (e.g., the number of episodes of nausea and/or emesis and/or vomiting after administration to a patient of a prescribed amount of chemotherapy, for example, a prescribed dose of a chemotherapeutic agent that is known to cause nausea or emesis). In some embodiments, reduce or inhibit can refer to the relative reduction of a side effect (i.e., nausea and/or emesis and/or vomiting) associated with a treatment for a condition or disease.

[106] As used herein, “prevention”, “prevent”, and/or “preventing”, are used interchangeably, and are intended to refer to all processes, including but not limited to pre-treatment, that keep something from happening or arising, or that make an event, such as emesis or nausea, unable to happen. As used herein, prevention is not intended to necessarily indicate a complete prevention of all disorder symptoms.

[107] The term “vomiting” as used herein refers to the contraction of the abdominal or diaphragm muscles to trigger the expulsion of stomach contents. Vomiting is also described as “throwing up.” When one vomits, one's abdominal muscles contract (squeeze) and push the contents of one's stomach out through their mouth. One might or might not feel nauseated.

[108] The term “retching” as used herein refers to emetic episodes without the passage of materials, e.g., the reverse movement of the stomach and esophagus without vomiting. The term “retching” as used herein also refers to the feeling of gagging without actually producing any vomit.

[109] As used herein, “therapeutically effective amount” refers to the amount of a compound that, when administered to a patient in need thereof, e.g., for the treatment of nausea and/or emesis, is sufficient to treat the said condition.

[110] As used herein, “titration” refers to a medication which is started at a low dose. The dose is gradually raised until the maximum desired dose is reached.

[111] As used herein, “tolerance” refers to the ability to comfortably endure treatment with a drug.

[112] As used herein, “treating” or “to treat” means attenuating, restraining, reversing, slowing, or stopping progression or severity of an existing condition, disease, disorder, or symptom.

[113] As used herein, the term “about”, unless the context require otherwise, means $\pm$ of an associated value.

[114] Other aspects and embodiments of the present disclosure will be apparent from the following Examples.

EXAMPLES

Example 1: An emetic potential study of Peptide A (SEQ ID NO:1), cisplatin, and Aprepitant following a single oral, subcutaneous, or intraperitoneal dose in male ferrets

Methods

[115] During the experimental period, adult (≥ 16 weeks) male ferrets ($n=5/\text{group}$ (0.9-1.8 kg), Marshall Farms) were individually housed in a temperature control-controlled environment (20-26°C), with a relative humidity of $50 \pm 20\%$, and a 12-hour light/12hour dark cycle. The animals were pre-treated with vehicle (Tris-HCl/0.02% PS-80) or Peptide A (SEQ ID NO:1)(at doses of 0.012 mg/kg, 0.125 mg/kg and 0.497 mg/kg, subcutaneous (SC)), 16-hrs prior to the administration of cisplatin (at a dose of 10 mg/kg, IP) or an anti-emetic therapeutic, Aprepitant (CAS170729-80-3) (at a dose of 2 mg/kg) or saline injection. Analysis of emetic episodes was measured by an observer blinded to treatment groups. The emetic episodes are characterized by strong rhythmic abdominal contractions associated with either oral expulsion from the gastrointestinal tract (i.e., vomiting) or without the passage of

materials (i.e., retching). Latency to the first emetic episode, total number of emetic episodes (with and without oral expulsion) intervals are quantified.

[116] Table 1. Emetic Behavior in Male Adult Ferrets

Treatment	Retching (Counts)	Vomiting (Counts)	Emetic Episodes (Counts)
Vehicle (Control)	0.40 ± 0.40	0.00 ± 0.00	0.00 ± 0.00
Cisplatin	51.20 ± 17.07*	5.00 ± 1.52*	56.20 ± 17.62*
Peptide A (High)	4.20 ± 2.56	0.20 ± 1.52	4.40 ± 2.73
Cisplatin + Peptide A (0.012 mg/kg)	22.60 ± 12.01	3.00 ± 1.30	25.60 ± 12.99
Cisplatin + Peptide A (0.125 mg/kg)	0.40 ± 0.40 [#]	0.00 ± 0.00 [#]	0.40 ± 0.40 [#]
Cisplatin + Peptide A (0.491 mg/kg)	1.00 ± 1.00 [#]	0.00 ± 0.00 [#]	1.00 ± 1.00 [#]
Cisplatin + Aprepitant	6.00 ± 4.39 [#]	1.40 ± 0.75 [#]	7.40 ± 5.11 [#]

[117] Ferrets were treated with cisplatin alone, or cisplatin in combination with Peptide A, or cisplatin in combination with Aprepitant, a known anti-emetic therapeutic. Male adult ferrets were pre-dosed with Peptide A Low (0.012 mg/kg), Medium (0.125 mg/kg), and High (0.491 mg/kg) dose 16-hours prior to the administration of cisplatin (10 mg/kg) or Aprepitant (n=5 per group). Data are presented as Mean ± SEM Statistical analysis was performed by a student T-Test. P<0.05 vs Vehicle* or Cisplatin[#].

[118] The data indicate that Peptide A (SEQ ID NO:1) does not cause emesis when administered alone, but pre-treatment with Peptide A attenuated emesis and retching induced by the known emetic agent cisplatin in adult male ferrets.

Example 2: A study to investigate the safety and tolerability of Peptide A (SEQ ID NO:1) when combined with a GLP-1 Receptor (GLP-1R) agonist in healthy participants

[119] A Phase 1, randomized, placebo-controlled, double-blind study investigated the safety and tolerability of a single dose (25 mg) of Peptide A (SEQ ID NO:1) or placebo in

combination with a GLP-1 receptor agonist, liraglutide, in healthy participants. It was hypothesized that pre-treatment with Peptide A (SEQ ID NO:1) may reduce adverse gastrointestinal (GI) events associated with the administration of a GLP-1 receptor agonist.

[120] **Study Inclusion Criteria.** Participants were healthy and between 11 and 60 years of age, inclusive, with a body weight of at least 55 kg and a BMI between 23 to 40 kg/m², inclusive. Female participants were not to be of childbearing potential and male participants were required to use appropriate contraception.

[121] **Study Exclusion Criteria.** Participants were excluded if they had a significant history of medical problems, including malignancy, infection with HIV and/or positive human immunodeficiency virus antibodies, evidence of hepatitis C and/or positive hepatitis C antibodies, or have knowledge of self or family history of multiple endocrine neoplasia Type2A or 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma. Participants were also excluded if they had undergone any form of bariatric surgery. Participants were also excluded if they had received any systemic or inhaled glucocorticoid therapy (excluding topical, intra-articular, and intraocular preparations) for more than 14 consecutive days within 2 weeks before screening, or if they intended to use over the counter or prescription medication 7 days before planned dosing, aside from vitamin/mineral supplements and acetaminophen. Participants were also excluded if they had any known allergies to liraglutide, Peptide A (SEQ ID NO:1), or any GIP or GLP-1R agonists, related compounds, or any formulated components of the study, or a history of significant atopy. Participants were excluded if they were currently enrolled in another clinical study not compatible with the current study, if they had participated in another clinical study within 30 days of screening (or longer if the study drug had a half-life longer than 30 days), or if they had previously completed or withdrawn from this study. Participants were also excluded if they had abnormalities in a 12-lead ECG that increases the risks associated with participating in the study, if they had serum AST or ALT more than 2x the ULN or TBL more than 1.5 ULN, if they had a serum triglyceride level at least 5 mmol/L (442.5 mg/dL), if they had amylase or lipase levels more than 2.5x ULN; or if they had a screening calcitonin more than 20 pg/mL. Participants were excluded if they donated blood in the past month or more than 450 mL of blood in the past 3 months. Participants were excluded if they had consumed alcohol in quantities of more than 21 units per week (males) or 14 units per week (females), or if they were unwilling to stop alcohol consumption 24 hours prior to dosing until discharge from the investigative site.

[122] **Study Design.** The study was conducted in two parts. Part A evaluated the tolerability of liraglutide administered daily (with within-cohort dose escalation every 2 days), followed by liraglutide in combination with a 25 mg dose of Peptide A (SEQ ID NO:1) or placebo in a parallel design, in a population of treatment-naïve healthy participants.

[123] An accelerated dose-escalation regimen was used to increase the dose of liraglutide every 2 days for each participant, from a starting dose of 0.6 mg to a final dose of 2.4 mg attained by Day 8, followed by a 2-week washout period (Part A, Period 1). This accelerated regimen was planned to increase the frequency of GI events, therefore allowing potential demonstration of a reduction of GI events with Peptide A (SEQ ID NO:1) pre-treatment. After the washout, the participants were re-admitted on the day prior to dosing and are randomly assigned to pre-treatment with a 25 mg dose of Peptide A (SEQ ID NO:1) or placebo on Day 1. The next day, the participants began liraglutide dosing (daily) for 8 days, similar to the first treatment period. An accelerated dosing regimen was used to increase the dose of liraglutide every 2 days for each participant (Part A, Period 2).

[124] Part B evaluated the tolerability of liraglutide administered daily to a population of treatment-naïve healthy participants with a 25 mg dose of Peptide A (SEQ ID NO:1) or placebo as pre-treatment in a crossover design, which provided within-patient repeated measures while avoiding sequence bias.

[125] The participants were randomly assigned to pre-treatment with either 25 mg dose of Peptide A (SEQ ID NO:1) or placebo on Day 1. The following day, participants began the daily liraglutide dosing for 8 days. Part B utilized an accelerated dosing regimen. The dose of liraglutide was increased every day for each participant, followed by an 8-week washout period. After the washout, participants crossed over to the alternate pre-treatment, either a 25 mg dose of Peptide A (SEQ ID NO:1) or placebo, identical to the first treatment period.

[126] The incretin response to 25 mg dose of Peptide A (SEQ ID NO:1) either alone or in combination with liraglutide was assessed by a graded glucose infusion (GGI), in Parts A and B. Intravenous glucose was used to induce hyperglycemia, which stimulated endogenous insulin secretion. By performing this procedure on different days during the dose-escalation schedule, the incretin effect from placebo, 25 mg dose of Peptide A (SEQ ID NO:1), 1.8 mg dose of liraglutide (Part A), 2.4 mg dose of liraglutide (Part B), and Peptide A + liraglutide could be measured. The GGI was performed in Part A Period 2, and in both treatment periods of Part B. The GGI was performed on Day 2, prior to the first dose of liraglutide

(measuring Peptide A (SEQ ID NO:1) or placebo response) and again on Day 6 (measuring the liraglutide or liraglutide + Peptide A (SEQ ID NO:1) response).

[127] **Participants.** Forty-four (44) participants were randomly assigned to study intervention, with 12 participants completing Part A and 32 participants completing Part B.

Table 2. Summary of number of events within each treatment group based on preferred term

Numbers in parentheses represent the mean number of events per participant in each group

Adverse Event (AE) Category	Preferred Term	Placebo (N=32)	25 mg of SEQ ID NO:1 (N=32)	P*
Gastrointestinal disorders	Abdominal discomfort	1 (0.03)	0 (0.00)	-
	Abdominal distension	11 (0.34)	7 (0.22)	0.238
	Constipation	2 (0.06)	1 (0.03)	0.310
	Diarrhoea	12 (0.38)	12 (0.38)	1.00
	Dyspepsia	3 (0.09)	0 (0.00)	-
	Eructation	2 (0.06)	1 (0.03)	0.654
	Flatulence	1 (0.03)	0 (0.00)	-
	Gastroesophageal reflux disease	14 (0.44)	5 (0.16)	0.005
	Nausea	11 (0.34)	6 (0.19)	0.185
	Vomiting	16 (0.50)	9 (0.28)	0.338
	All GI	73 (2.28)	41 (1.28)	0.022
General disorders	Early satiety	5 (0.16)	8 (0.25)	0.510
Metabolism and nutrition disorders	Decreased appetite	21 (0.66)	15 (0.47)	0.095

*P-values are from a generalized linear model assuming a negative binomial distribution comparing mean events per patient in Placebo vs. Protein A (SEQ ID NO:1) groups after accounting for repeated measures on the same patient. Some p-values are not available due to low event counts.

[128] Table 3. Frequency (%) of participants with ≥ 1 Treatment-Emergent Adverse Events (TEAE) based on preferred term

AE Category	Preferred Term	Placebo (N=32)	25 mg of SEQ ID NO:1 (N=32)	P [†]
Gastrointestinal disorders	Abdominal discomfort	1 (3.1%)	0 (0.0%)	0.317
	Abdominal distension	9 (28.1%)	6 (18.8%)	0.257
	Constipation	2 (6.3%)	1 (3.1%)	0.317
	Diarrhoea	3 (9.4%)	5 (15.6%)	0.317
	Dyspepsia	3 (9.4%)	0 (0.0%)	
	Eructation	1 (3.1%)	1 (3.1%)	1.00
	Flatulence	1 (3.1%)	0 (0.0%)	
	Gastrooesophageal reflux disease	11 (34.4%)	3 (9.4%)	0.011
	Nausea	10 (31.3%)	5 (15.6%)	0.132
	Vomiting	5 (15.6%)	3 (9.4%)	0.317
	All GI	23 (71.9%)	16 (50.0%)	0.089
General disorders	Early Satiety	5 (15.6%)	5 (15.6%)	1.00
Metabolism and nutrition disorders	Decreased appetite	19 (59.4%)	14 (43.8%)	0.132

[†]P-values are from a McNemar's test comparing paired binary data between Protein A (SEQ ID NO:1) and Placebo groups. Some p-values are not available due to low event counts.

[129] **Results.** Thirty-two healthy participants were dosed and 31 completed both periods of the trial. All 32 patients were included for analyses of safety data. In the placebo-treated phase of the trial, the total number of gastrointestinal adverse events was 73 (2.28 events per participant on average); 23/32 (72%) participants experienced gastrointestinal adverse events. With pre-treatment with the GIP receptor agonist, the frequency of gastrointestinal adverse events was 41 (1.28 events per participant on average); 17/32 (53%) participants experienced gastrointestinal adverse events (p=0.02 comparing total event rates with Peptide A vs placebo; no evidence of sequence effect).

[130] The number of participants affected by the three most common GI events (nausea, vomiting, and gastro-esophageal reflux) decreased by approximately 20-65%. The total

number of the three most common GI events (nausea, vomiting, and gastro-esophageal reflux) also decreased by approximately 45-65%.

Example 3: A Phase 1b, 2-Part, double-blind, multiple-ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of Peptide B (SEQ ID NO:2) in participants with Type 2 Diabetes Mellitus (T2DM)

[131] A Phase 1b, randomized, single centre, double-blind, 2-part multiple-ascending dose (MAD) study of Peptide B (SEQ ID NO:2) was performed in participants with T2DM. The study consisted of a screening period, a lead-in period, a treatment period, and a follow-up period. Part A of the study consisted of 2 cohorts (7.5 mg dose, once weekly (QW) and a 20 mg dose, QW, with approximately 9 participants in each cohort randomized to Peptide B (SEQ ID NO:2) or placebo in a 6:3 manner, and a 1.5 mg dose of dulaglutide (QW) was added to the treatment regimen at the ninth week for all participants.

[132] Part B of the study consisted of 3 cohorts with participants randomized in a 2:2:1 manner to receive a 1.5 mg dose of dulaglutide (QW) + placebo matching Peptide B, 20 mg dose of Peptide B (SEQ ID NO:2) (QW) + 1.5 mg dose of dulaglutide QW (24 participants) or Peptide B 20 mg QW + placebo matching dulaglutide (12 participants).

[133] Inclusion Criteria. To be considered for inclusion in the study, participants were required to be healthy and be between 18 and 70 years of age inclusive, with a body weight of up to 150 kg and BMI within the range of 23 to 45 kg/m², inclusive. Female participants could not be of child-bearing potential and male participants agreed to use highly effective/effective methods of contraception.

[134] **Study Design.** The study was conducted in two parts. Part A consisted of 2 cohorts (7.5 mg QW and 20 mg QW) with approximately 9 participants in each cohort randomized to either Peptide B or placebo in a 6:3 manner, and dulaglutide 1.5 mg QW was added to the treatment regimen from the ninth week onwards for all participants. Part B consisted of 3 cohorts with participants randomized in a 2:2:1 manner to receive dulaglutide 1.5 mg QW + placebo (24 participants), Peptide B 20 mg QW + dulaglutide 1.5 mg QW (24 participants) or Peptide B 20 mg QW + placebo (12 participants), respectively.

[135] **Part A.** Eligible participants were randomized in a 6:3 manner to receive subcutaneous injections of Peptide B or placebo QW. The doses for Part A were Cohort 1: 7.5 mg and Cohort 2: 20 mg. The treatment period was 12 weeks. All participants received dulaglutide 1.5 mg QW from the ninth week onwards.

[136] The primary objective of Part A was to investigate the safety and tolerability following SC administration of multiple QW doses of Peptide B versus placebo with and without dulaglutide in participants with T2DM. The endpoints were treatment-emergent adverse events (TEAE) and serious adverse events (SAEs). The secondary objectives of Part A were to characterize the PK profile following multiple QW doses and to characterize the effects on glucose control and glucagon secretion. The endpoints were C_{max} and AUC, changes from baseline in fasting and post-meal glucose during sMMTT (total and incremental AUC_{0-240 min}), changes from baseline in HbA1c, changes in baseline in glucagon concentration at fasting and post-meal during sMMTT (total and incremental AUC_{0-240 min}). The exploratory objectives included: to characterize the effects on body weight and lipid parameters following multiple QW doses; to characterize the effect on appetite and food intake; to characterize Peptide B immunogenicity following multiple QW doses; to characterize the effects of Peptide B on blood markers of target engagement. The exploratory endpoints included: changes from baseline in body weight, waist circumference, body composition (BIA) and lipid parameters; changes in fasting appetite (VAS); changes in appetite (VAS) score during sMMTT; incidence of treatment-emergent ADAs; CTX-1, and pancreatic polypeptide levels.

[137] **Part B.** Eligible participants were randomized in a 2:2:1 manner to receive SC injections of dulaglutide 1.5 mg + placebo, Peptide B + dulaglutide 1.5 mg QW or Peptide B + placebo, respectively. The treatment period was 12 weeks.

[138] The primary objective of Part B was to characterize the effects of Peptide B on insulin secretion and insulin sensitivity combined outcome. The primary endpoint of Part B was the change in total clamp disposition index (cDI).

[139] The secondary objectives of Part B included: investigating the safety and tolerability following SC administration of multiple QW doses of Peptide B, dulaglutide, or Peptide B + dulaglutide in participants with T2DM; to characterize the effects on insulin secretion, insulin sensitivity, glucose control, and glucagon secretion. The secondary endpoints of Part B included frequency of TEAEs and SAEs, changes from baseline in ISR and β -cell glucose sensitivity (GS) from hyperglycaemic clamp, change from baseline in hyperinsulinaemic euglycaemic clamp M-value; change from baseline in fasting and post-meal glucose during sMTT (total and incremental AUC_{0-240 min}); change from baseline in HbA1c; change from baseline in glucagon concentration at fasting and post-meal during sMMTT (total and incremental AUC_{0-240 min}).

[140] The exploratory objectives of Part B were to characterize effects on body weight and lipid parameters following multiple QW doses; to characterize the effect on appetite and food intake; to characterize Peptide B immunogenicity following multiple QW doses; to characterize the effects on insulin secretion. The exploratory endpoints of Part B include: change from baseline in body weight, waist circumference, body composition (BIA), lipid parameters; changes in fasting appetite (VAS); changes in appetite (VAS) score during sMMTT; incidences of treatment-emergent ADAs; changes from baseline in insulin response to arginine (incremental AUC_{arginine}_{0-10 min} and incremental AUC_{arginine}_{0-30 min}) from hyperglycaemic clamp; change in β -cell GS from sMMT; changes from baseline in ISRg from sMMTT; CTX-1, pancreatic polypeptide levels.

[141] **Results.** In Part A, very few adverse events of nausea (n = 1) and vomiting (n = 0) occurred after a treatment regimen of dulaglutide and Peptide B. In Part B, there were numerically less event of nausea and vomiting in those participants treated with dulaglutide and Peptide B than those participants treated with dulaglutide and placebo.

Table 4. Summary of Number of Events within Each Treatment Group Based on Preferred Term - Part A Results

Adverse Effects (AE) Preferred Term	Placebo (n=6)	7.5 mg Peptide B (n=6)	20 mg Peptide B (n=6)
Total Gastrointestinal Disorders	6 (100%)	3(50.0%)	4(66.7%)
Nausea	0 (0.0%)	1 (16.7%)	0 (0.0%)
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5. Summary of Number of Events within Each Treatment Group based on Preferred Term

Part B Results

Adverse Effects (AE) Preferred Term	Placebo + 1.5 mg dulaglutide (n=29)	20 mg Peptide B + Placebo (n=15)	20 mg Peptide B + 1.5 mg dulaglutide (n=28)
Total Gastrointestinal Disorders	16 (55.2%)	5 (33.3%)	17 (60.7%)
Nausea	5 (17.2%)	1 (6.7%)	3 (10.7%)
Vomiting	4 (13.8%)	0 (0.0%)	2 (7.1%)

SEQUENCE LISTING**Peptide A (SEQ ID NO:1)**

Y-Aib-EGTFISDYSI- α MeL-LD-Orn-IHQ-Aib-DFVEYK ((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ -Glu)-CO-(CH₂)₁₈-CO₂H) LEGGPSSGAPPPS-NH₂

Peptide B (SEQ ID NO:2)

Y-Aib-EGTFISDYSI- α MeL-LDKK ((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ -Glu)-CO-(CH₂)₁₈-CO₂H) HQ-Aib-DFVE-4-Pal-LLEAGPSSGAPPPS-NH₂

Semaglutide (SEQ ID NO:3)

H-Aib-EGTFTSDVSSYLEGQAAK ((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)-CO-(CH₂)₁₆-CO₂H) EFIAWLVRGRG

Liraglutide (CAS Registry Number: 204656-20-2) (SEQ ID NO:4)

HAEGTFTSDVSSYLEGQAAK (γ Glu-CO-(CH₂)₁₄-CH₃) EFIAWLVRGRG

Dulaglutide (SEQ ID NO:5)

Dulaglutide is a human GLP-1 receptor agonist which comprises a dimer of a GLP-1 analog fused at its C-terminus via a peptide linker to the N-terminus of an analog of an Fc portion of an immunoglobulin, and is identified by CAS registry number 923950-08-7, which provides the following chemical name: 7-37-Glucagon-like peptide I [8-glycine,22-glutamic acid,36-glycine] (synthetic human) fusion protein with peptide (synthetic 16-amino acid linker) fusion protein with immunoglobulin G4 (synthetic human Fc fragment), dimer. Each monomer of dulaglutide has the amino acid sequence set forth in SEQ ID NO:13:

HGEGTFTSDVSSYLEEQAAKEFIAWLVKGGGGGGSGGGGSAESKYGPCCPPCPAPE
AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ
FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQE
GNVFSCSVMHEALHNHYTQKSLSLGLG

Mazdutide (SEQ ID NO:6)

H-Aib-QGTFTSDYSKYLDEKKAK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)-CO-(CH₂)₁₈-CO₂H)EFVEWLLEGGPSSG-NH₂

Long-Acting Amylin Receptor Agonist (SEQ ID NO:7)

γE-CNTATCATG-Orn-LAE-αMeF-LVRSSN-NMeN-FGPKLPPTTEVGSNTY-NH₂

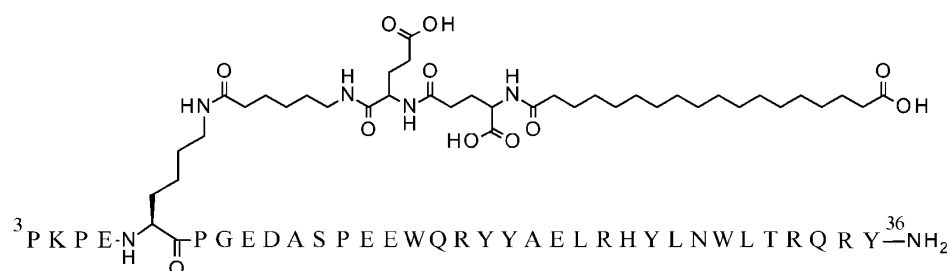
wherein there is a thioacetal bridge between the cysteines at positions 2 and 7; and

wherein the lysine at position 26 is attached to a fatty acid linker moiety according to the formula (γE)₂-CO-(CH₂)₁₈-CO₂H

Dual Agonist of Calcitonin and Amylin Receptors (SEQ ID NO:8)

Acetyl-ASHLSTAVLGK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)-CO-(CH₂)₁₈-CO₂H)LS-Aib-ELHKLEDYPRTDVGAESP-NH₂

Peptide Tyrosine-Tyrosine (PYY) Analog (SEQ ID NO:9)



CLAIMS

1. A method for treating or preventing nausea or emesis in a patient, the method comprising administering a therapeutically effective amount of a GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.
2. The method of claim 1, wherein the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is about 0.3 to 30 mg.
3. The method of claim 1, wherein the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is about 5.0 to 30 mg.
4. The method of any one of claims 1-2, wherein the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is 7.5 mg.
5. The method of any one of claims 1-2, wherein the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is 20 mg.
6. The method of any one of claims 1-2, wherein the therapeutically effective amount of the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is 25 mg.
7. The method of any one of claims 1 to 6, wherein the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is formulated into a medicament.
8. The method of any one of claims 1 to 7, wherein the treatment of nausea or emesis is in the patient taking a medicament to treat a metabolic syndrome disorder.
9. The method of claim 8, wherein the metabolic syndrome disorder is Type 2 diabetes mellitus or obesity.
10. The method of any one of claims 8-9, wherein the medicament to treat the metabolic syndrome disorder is selected from the group consisting of a GLP-1 receptor agonist peptide, a dual agonist peptide of the GLP-1 and glucagon (GCG)

receptors, a long-acting-agonist peptide of the amylin receptor, a dual amylin and calcitonin receptor agonist peptide, a monoclonal antibody directed to the leptin receptor, a urocortin peptide, or a peptide tyrosine-tyrosine (PYY) analog to the patient.

11. The method of claim 10, wherein the medicament to treat the metabolic syndrome disorder is selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9, or a pharmaceutically acceptable salt thereof.

12. The method of any one of claims 10-11, wherein the patient's tolerance to nausea or emesis-inducing treatment of the metabolic syndrome disorder is improved.

13. The method of any one of claims 10 to 12, wherein the medicament to treat the metabolic syndrome disorder is administered without titration.

14. The method of any one of claims 1 to 7, wherein the treatment of nausea or emesis is in the patient taking a chemotherapeutic agent.

15. The method of claim 14, wherein the chemotherapeutic agent is selected from the group consisting of anthracycline, cyclophosphamide, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, epirubicin, fam-trastuzumab deruxtecan-nxki, ifosfamide, mechlorethamine, melphalan, sacituzumab govitecan-hzly, and streptozocin.

16. The method of claim 14, wherein the chemotherapeutic agent is selected from the group consisting of aldesleukin, amifostine, bendamustine, busulfan, carboplatin, carmustine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, dinutuximab, doxorubicin, dual-drug liposomal encapsulation of cytarabine and daunorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, irinotecan (liposomal), lurbinectedin, melphalan, methotrexate, mirvetuximab soratansine-gynx, naxitamab-gqgk, oxaliplatin, romidepsin, temozolomide, and trabectedin.

17. The method of claim 15, wherein the chemotherapeutic agent is cisplatin.

18. The method of claim 15, wherein the chemotherapeutic agent is a combination of cyclophosphamide and an anthracycline.

19. The method of claim 18, wherein the anthracycline is selected from the group consisting of doxorubicin, daunorubicin, and idarubicin.

20. The method of any one of claims 14 to 19, wherein the patient's tolerance to the nausea or emesis inducing treatment with the chemotherapeutic agent is improved.

21. The method of any one of claims 14 to 20, wherein the chemotherapeutic agent is administered without titration.
22. The method of any one of claims 1 to 21, wherein the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered subcutaneously, intravenously, intramuscularly, intraperitoneally, orally, or via inhalation.
23. The method of any one of claims 1 to 22, wherein the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered to the patient one time, once weekly, twice monthly, once every three weeks, once monthly, or once yearly.
24. The method of claim 23, wherein the GIP receptor agonist peptide comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, is administered subcutaneously to the patient once weekly.
25. Use of a pharmaceutical composition comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for treating or preventing nausea or emesis in a patient.
26. Use of the compound of comprising SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of nausea or emesis in a patient.
27. A pharmaceutical composition comprising the compound of SEQ ID NO:1 or SEQ ID NO:2, or a pharmaceutically acceptable salt thereof, for use in treating or preventing nausea or emesis in a patient.