GLUCAGON-LIKE PEPTIDE 2 (GLP-2) ANALOGS FOR THE TREATMENT OF GRAFT VERSUS HOST DISEASE

RELATED APPLICATIONS

[0001] This application claims the priority to, and benefit of, U.S. Provisional Application No. 63/571,403, filed on March 28, 2024, the contents of which are incorporated by reference in its entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (VECT-006_001WO_SeqListST26.xml; Size: 3,090 bytes; and Date of Creation: March 19, 2025) is herein incorporated by reference in its entirety.

BACKGROUND

[0003] Graft versus Host Disease (GvHD) is a condition that occurs following a transplant in a subject. GvHD is most commonly observed in the context of an allogeneic transplants, including hematopoietic stem cell transplantation (AHCT) for the treatment of a blood cancer. However, there is increasing evidence that GvHD also occurs within the context of autologous transplants (Hammami *et al., Gastroenterol Res.*, 2018, 11(1):52-57; Cogbill *et al. Modern Pathology*, 2011, 24:117-125). GvHD occurs when immune cells present in the allogeneic transplant perceive the transplant recipient's tissues as foreign and proceed to attack the recipient's tissues. GvHD may manifest as either acute GvHD or chronic GvHD. Acute GvHD is typically characterized by inflammation and tissue damage in the skin, oral and genital mucosa, eyes, gut, liver, lungs, joints, and muscles. Chronic GvHD can induce the same type of damage, but over longer periods can also cause damage to connective tissue of exocrine glands, tissue fibrosis and limitation of joint motility, fibrosis of the lungs and liver, immune dysregulation and autoimmunity. In particular, acute GvHD of the gastrointestinal tract can result in severe intestinal inflammation, sloughing of the mucosal membrane, severe diarrhea, abdominal pain, nausea and vomiting. Severe manifestations of acute gastrointestinal GvHD are often seen in patients with poorer, post-transplant prognoses, and the GI tract is involved in almost all fatal cases of GvHD.

[0004] First-line treatment of acute gastrointestinal GvHD typically comprises the use of systemic and/or oral non-absorbable corticosteroids. However, a large number of patients fail to respond to first-line therapy. Ruxolitinib (RUX), a JAK inhibitor, was approved for treating

steroid-refractory GvHD in 2019 by the United States Food and Drug Administration. However, a significant number of patients do not respond to RUX, or lose the initial response to RUX over continued administration.

[0005] Thus, there exists a need in the art for compositions and methods directed to the treatment and prevention of GvHD, particularly for acute gastrointestinal GvHD, including in subjects that have received an AHCT.

SUMMARY

[0006] The present disclosure provides, in some aspects, apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment of Graft versus Host Disease (GvHD) in a subject, wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered once weekly, wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered concurrently with ruxolitinib, and wherein the administration of apraglutide or pharmaceutically acceptable salt thereof results in a decreased lower gastrointestinal (lower GI) MAGIC clinical stage compared to baseline for at least 90 days after initiation of treatment.

[0007] In some aspects, the present disclosure provides a method of treating Graft versus Host Disease (GvHD) in a subject, the method comprising administering the apraglutide, or a pharmaceutically acceptable salt thereof, once weekly to the subject, wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered concurrently with ruxolitinib, and wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof results in a decreased lower gastrointestinal (lower GI) MAGIC clinical stage compared to baseline for at least 90 days after initiation of treatment.

[0008] In some embodiments of the above aspects, (a) the subject has a body weight of less than 50 kg, and the apraglutide is administered at a dose of about 2.5 mg; (b) the subject has a body weight of about 50 kg to about 60 kg, and the apraglutide is administered at a dose of about 2.5 mg or about 5 mg; (c) the subject has a body weight of about 60 kg to about 80 kg, and the apraglutide is administered at a dose of about 4 mg or about 7.5 mg; or (d) the subject has a body weight of greater than 80 kg, and the apraglutide is administered at a dose of about 5 mg or about 10 mg.

[0009] In some embodiments of the above aspects, (a) the subject has a body weight of less than 50 kg, and the apraglutide is administered at a dose of about 1.5 mg; (b) the subject has a body weight of about 50 kg to about 60 kg, and the apraglutide is administered at a dose of about 1.5 mg or about 3.6 mg; (c) the subject has a body weight of about 60 kg to about 80 kg, and the apraglutide is administered at a dose of about 2.7 mg or about 5.5 mg; or (d) the subject

has a body weight of greater than 80 kg, and the apraglutide is administered at a dose of about 3.6 mg or about 7.6 mg.

[0010] Some embodiments of the above aspects further comprise administering one or more systemic steroids to the subject.

[0011] In some embodiments of the above aspects, the GvHD is acute GvHD. In some embodiments, the GvHD is acute gastrointestinal GvHD. In some embodiments, the GvHD is steroid-refractory.

[0012] In some embodiments of the above aspects, the baseline is stage 1-4 GvHD according to the MAGIC scale for lower GI, and after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased to stage 0.

[0013] In some embodiments of the above aspects, the baseline is stage 1-4 GvHD according to the MAGIC scale for lower GI, and after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased by at least one stage.

[0014] In some embodiments of the above aspects, the subject has a complete response to treatment.

[0015] In some embodiments of the above aspects, the subject has a partial response to treatment.

[0016] In some embodiments of the above aspects, the administration of apraglutide or a pharmaceutically acceptable salt thereof results in a decreased all-organ MAGIC clinical score for at least about 90 days after initiation of treatment.

[0017] In some embodiments of the above aspects, the administration of apraglutide or a pharmaceutically acceptable salt thereof maintains the decreased MAGIC lower GI stage for at least about 3× as many days as a subject administered ruxolitinib only.

[0018] In some embodiments of the above aspects, the administration of apraglutide or a pharmaceutically acceptable salt thereof decreases relapse compared to a subject administered ruxolitinib only.

[0019] In some embodiments of the above aspects, the administration of apraglutide or a pharmaceutically acceptable salt thereof decreases mortality compared to a subject administered ruxolitinib only.

[0020] In some embodiments of the above aspects, the administration of apraglutide or a pharmaceutically acceptable salt thereof decreases non-relapse mortality compared to a subject administered ruxolitinib only.

[0021] In some embodiments of the above aspects, the administration of apraglutide or a pharmaceutically acceptable salt thereof increases overall survival compared to a subject administered ruxolitinib only.

[0022] In some embodiments of the above aspects, the GvHD is steroid-naïve.

[0023] In some embodiments of the above aspects, the GvHD is chronic GvHD.

[0024] In some embodiments of the above aspects, the apraglutide or pharmaceutically acceptable salt thereof is administered prior to the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with a transplant.

[0025] In some embodiments of the above aspects, the subject has been previously administered a transplant, optionally wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered to the subject after the subject has been administered a transplant.

[0026] In some embodiments of the above aspects, the subject has been previously administered radiation therapy, chemotherapy, radiomimetic therapy, or any combination thereof, in connection with a transplant, optionally wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof.

[0027] In some embodiments of the above aspects, the administration of apraglutide or a pharmaceutically acceptable salt thereof prevents and/or attenuates a reduction in colon length in a subject following a transplant; and/or a conditioning therapy and a transplant.

[0028] In some embodiments of the above aspects, the transplant comprises hematopoietic stem cells derived from bone marrow, peripheral blood, umbilical cord blood or any combination thereof, optionally wherein the transplant comprises T-cells, and optionally wherein the T-cells are chimeric antigen receptor (CAR) T-cells.

[0029] In some embodiments of the above aspects, the radiation therapy comprises total body irradiation.

[0030] In some embodiments of the above aspects, the pharmaceutically acceptable salt of apraglutide is the sodium salt of apraglutide.

[0031] In some embodiments of the above aspects, the apraglutide or pharmaceutically acceptable salt thereof is administered by subcutaneous injection.

[0032] In some embodiments of the above aspects, the transplant is an allogeneic transplant or an autologous transplant.

[0033] Any of the above aspects, or any other aspect described herein, can be combined with any other aspect described herein.

[0034] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0035] In the specification, the singular forms also include the plural unless the context clearly dictates otherwise; as examples, the terms "a," "an," and "the" are understood to be singular or plural and the term "or" is understood to be inclusive. By way of example, "an element" means one or more element. Throughout the specification the word "comprising," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps. Unless otherwise clear from the context, all numerical values provided herein are modified by the term "about." Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive and covers both "or" and "and".

[0036] Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The references cited herein are not admitted to be prior art to the claimed disclosure. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting. Other features and advantages of the disclosure will be apparent from the following detailed description and claim.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The features of the present disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0038] **FIG. 1** is a schematic depiction of a study of apraglutide in treating subjects with Graft versus Host Disease (GvHD).

[0039] **FIG. 2A** is a series of line graphs demonstrating response on the lower gastrointestinal (lower GI) MAGIC score for GvHD patients administered apraglutide at low dose, high dose, or all patients, up to day 91 of treatment. **FIG. 2B** is a line graph demonstrating response on

the lower GI MAGIC score for GvHD patients for all patients administered apraglutide up to day 91 of treatment.

[0040] FIG. 3 is a series of line graphs demonstrating response on the all-organ MAGIC score for GvHD patients administered apraglutide at low dose, high dose, or all patients, up to day 91 of treatment.

[0041] FIG. 4A is a diagram depicting individual patient response on lower GI MAGIC score between days 28, 56, and 91 of apraglutide treatment. **FIG. 4B** is a chart depicting individual patient response on lower GI MAGIC score at each clinical visit, up to 1-year. **FIG. 4C** is a diagram depicting individual patient response on all-organ MAGIC score between days 28, 56, and 91 of apraglutide treatment. **FIG. 4D** is a chart depicting individual patient response on all-organ MAGIC score at each clinical visit, up to 1-year.

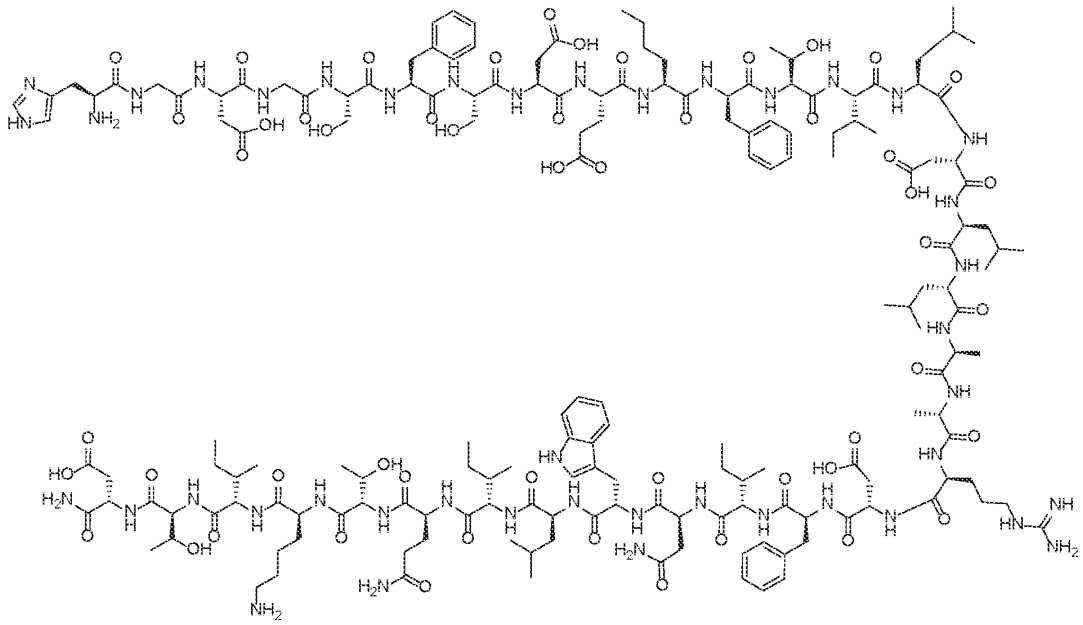
DETAILED DESCRIPTION

[0042] The present disclosure is directed to methods of treating graft versus host disease (GvHD) using GLP-2 analogs such as apraglutide, or a pharmaceutically acceptable salt thereof. The disclosure is based, in part, on the discovery that a GLP-2 analog, *e.g.*, apraglutide, or a pharmaceutically acceptable salt thereof, when administered to a subject with GvHD in combination ruxolitinib provides a significant benefit to the subject. Subjects receiving a combination of apraglutide and ruxolitinib demonstrates a remarkable improvement in the gastrointestinal (GI) system, *e.g.*, as measured by MAGIC score and MAGIC staging of the lower GI. The improved effect to the GI lasts at least 91 days.

[0043] Various aspects of the present disclosure are set forth below in sections; however, aspects of the disclosure described in one particular section are not to be limited to any particular section.

[0044] To facilitate an understanding of the present disclosure, a number of terms and phrases are defined below.

[0045] Unless explicitly indicated otherwise, the term "apraglutide," refers to the compound which has the following structure:



[0046] As would be appreciated by the skilled artisan, apraglutide is a GLP-2 agonist having an amino acid sequence of His-Gly-Asp-Gly-Ser-Phe-Ser-Asp-Glu-Nle-D-Phe-Thr-Ile-Leu-Asp-Leu-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Asn-Trp-Leu-Ile-Gln-Thr-Lys-Ile-Thr-Asp (SEQ ID NO: 1), wherein Nle is norleucine and D-Phe is the D-amino acid phenylalanine.

[0047] Apraglutide, and its preparation, are disclosed in PCT Application Publication No. WO2011/050174, US Patent No. 8,580,918, US Patent Publication No. 2022-0000985A1, and PCT Application Publication No. WO2021/252659. These publications are incorporated by reference herein in their entireties.

[0048] As used herein, the term "GLP-2 analog" refers collectively to an analog of a naturally occurring GLP-2 in a vertebrate, which elicits similar or comparable activity to the naturally occurring GLP-2, but is structurally altered, relative to a given vertebrate GLP-2, by at least one amino acid addition, deletion, substitution, modification, and/or by incorporation of one or more amino acid(s) with a blocking group. Such analogs generally have an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identical to that of either GLP-2 or a fragment of GLP-2 having the same number of amino acid residues. GLP-2 analogs are known in the art and can include, for example and without limitation, human [Gly^2] GLP-2, glepaglutide, NM-003, teduglutide, apraglutide, and elsiglutide, and pharmaceutically acceptable salts thereof.

[0049] Unless explicitly indicated otherwise, the terms "approximately" and "about" are synonymous. As used herein, the terms "approximately" and "about" refer to a ±10% variation from the nominal value unless otherwise indicated or inferred.

[0050] As would be appreciated by the skilled artisan, the terms "Graft versus Host Disease" or "GvHD" refer to the condition that occurs in a subject following an allogeneic or autologous transplant (*e.g.*, a HSCT) in which immune cells presented in the allogeneic or autologous transplant material (referred to as the "graft") attack the transplant recipient's own tissues. As would be appreciated by the skilled artisan, GvHD may be classified using MAGIC grading scale as described in *Biol Blood Marrow Transplant. 2016;22(1):4-10.*

[0051] As would be appreciated by the skilled artisan, the terms "acute Graft versus Host Disease", "acute GvHD", "classic acute Graft versus Host Disease" and "classic acute GvHD" refer to Graft versus Host Disease that develops in a transplant recipient within about 100 days following transplantation and manifests with clinical features that are typically associated with acute Graft versus Host Disease, including, but not limited to inflammation and tissue damage in the skin, oral and genital mucosa, eyes, gut, liver, lungs, joints, and muscle.

[0052] As would be appreciated by the skilled artisan, the terms "late acute Graft versus Host Disease" or "late acute GvHD" refer to the conditions of persistent acute Graft versus Host Disease, recurrent acute Graft versus Host Disease, and/or new-onset acute Graft versus Host Disease, which are forms of Graft versus Host Disease that manifest with the clinical features of acute Graft versus Host Disease, but more than 100 days after the transplantation.

[0053] As would be appreciated by the skilled artisan, the terms "acute gastrointestinal Graft versus Host Disease" and "acute gastrointestinal GvHD" refer to any form of acute GvHD described above that manifests in a subject with gastrointestinal symptoms and/or damage, including, but not limited to, diarrhea, abdominal pain, mucositis, mucosal ulceration, nausea, shortening of the colon, shortening of the small intestine.

[0054] As would be appreciated by the skilled artisan, the term "steroid-refractory", "steroid-refractory GvHD", and "SR-GvHD" refers to GvHD that has been previously treated using steroid therapy, but has become non-responsive to the steroid therapy. Thus, in a non-limiting example, steroid-refractory acute gastrointestinal GvHD refers to acute gastrointestinal GvHD that has been previous treated using a steroid therapy, but has become non-responsive to steroid therapy. In some aspects, subjects with steroid-refractory GvHD are administered a pharmaceutical composition comprising ruxolitinib. In some aspects, subjects with steroid-refractory GvHD are administered a pharmaceutical composition comprising apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, to a subject with steroid-refractory

GvHD is administered a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of immunosuppressive therapy. In some aspects, to a subject with steroid-refractory GvHD is administered a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of ruxolitinib and/or systemic steroids.

[0055] As would be appreciated by the skilled artisan, the term "steroid-naïve" refers to GvHD that has not been previously treated using a steroid therapy. Thus, in a non-limiting example, steroid-naïve acute gastrointestinal GvHD refers to acute gastrointestinal GvHD that has not been previously treated using a steroid therapy.

[0056] As would be appreciated by the skilled artisan, the terms "chronic Graft versus Host Disease" or "chronic GvHD" refer to Graft versus Host Disease that develop more than 100 days after the transplantation and manifests with clinical features that are typically associated with chronic Graft versus Host Disease, including, but not limited to, damage to connective tissue of exocrine glands, tissue fibrosis and limitation of joint motility, fibrosis of the lungs and liver, immune dysregulation and autoimmunity.

[0057] As would be appreciated by the skilled artisan, the term "chronic gastrointestinal Graft versus Host Disease" and "chronic gastrointestinal GvHD" refers to any form of chronic GvHD described above that manifests in a subject with gastrointestinal symptoms and/or damage, including, but not limited to, diarrhea, abdominal pain, mucositis, mucosal ulceration, nausea, shortening of the colon, shortening of the small intestine.

[0058] As would be appreciated by the skilled artisan, the term "Overlap Syndrome" refers to Graft versus Host Disease that can present at any time post-transplant and that manifests with clinical features of both acute Graft versus Host Disease and chronic Graft versus Host Disease.

[0059] As would be appreciated by the skilled artisan, the terms "upper gut Graft versus Host Disease", "upper gut GvHD", "upper gut GvHD phenotype" and "upper gut phenotype of GvHD" refer to Graft versus Host Disease that presents with persistent loss of appetite, satiety, nausea, vomiting, and weight loss, with variable amounts of diarrhea. The presentation can be indolent, and therapy with prednisone at doses of 1 mg/kg/day plus topical oral corticosteroid is effective. In some aspects, the upper gut GvHD phenotype does not progress to the mid-lower gut GvHD phenotype. In some aspects, the upper gut GvHD phenotype is limited to GvHD grade I.

[0060] As would be appreciated by the skilled artisan, the terms "mid-lower gut Graft versus Host Disease", "mid-lower gut GvHD", "mid-lower gut GvHD phenotype" and "mid-lower

gut phenotype of GvHD" refer to Graft versus Host Disease that presents with secretory, protein-rich and bile salt diarrhea and abdominal pain resulting from gut distention. In some aspects, mid-lower gut GvHD is severe, wherein the subject presents with the entire small intestine and colon as edematous and inflamed, with larger diarrheal volumes and evidence of mucosal ulceration and bleeding. In some aspects, subjects with severe mid-lower gut GvHD require prolonged hospitalization for supportive care including total parenteral nutrition and pain control. In some aspects, subjects with severe mid-lower gut GvHD require the standard initial therapy comprising prednisone with or without other immune suppressive therapies.

[0061] As would be appreciated by the skilled artisan, the term "GI-aGVHD response" refers to a decrease of one stage in the signs and symptoms of GI-aGVHD without any intercurrent events of discontinuation of the assigned apraglutide treatment, institution of new systemic therapy, or death. In some aspects, a complete GI-aGVHD response refers to the resolution of all GI-aGVHD signs and symptoms GVHD without any intercurrent events of discontinuation of the assigned apraglutide treatment, institution of new systemic therapy, or death. In some aspects, a partial response refers to an improvement of 1 stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response or non-response of aGVHD. In some aspects, a GI-aGVHD flare refers to any increase in signs or symptoms of GI-aGVHD that is sustained for >24 h after an initial response and requires re-escalation of immunosuppressive therapy (*e.g.*, corticosteroid, calcineurin inhibitors, and/or ruxolitinib dosing).

[0062] As used herein, the term "subject" includes any living organism that has GvHD, or is at a risk of developing GvHD. In some aspects, the term "subject" refers to a mammal that has GvHD, or is at a risk of developing GvHD. In some aspects, the term subject refers to a human being that has GvHD, or is at a risk of developing GvHD. A human that is at risk of developing GvHD can be a human that is to receive, is currently receiving, or has previously received an transplant (allogeneic or autologous). A human that is at risk of developing GvHD can be a human that is to receive, is currently receiving, or has previously received a conditioning therapy in connection with an HSCT.

[0063] As used herein, the term "patient" is meant to be synonymous and may be used interchangeably with "subject," unless explicitly indicated otherwise.

[0064] As used herein, the term "allogeneic" refers to biological material isolated from a donor that is to be transplanted into a recipient, wherein the donor and the recipient are two different subjects.

[0065] As used herein, the term "autologous" refers to biological material isolated from a donor that is to be transplanted into a recipient, wherein the donor and the recipient is the same subject.

[0066] As used herein, the term "conditioning therapy" refers to the use of radiation therapy, such as total body irradiation, chemotherapy, or radiomimetic therapy that typically administered to a subject prior to an HSCT. As would be appreciated by the skilled artisan, the aims of conditioning therapy include: a) eradication of the underlying disease (*e.g.*, cancer, a blood cancer) that is to be treated using by the HSCT; b) creation of space in the bone marrow for donor stem cells to engraft; and c) immunosuppression to decrease the risk of rejection of the donor cells by the host cells. As used herein, conditioning therapy can refer to any conditioning therapy known in the art, including, but not limited to, total body irradiation. The term "radiomimetic therapy" refers to any drug, compound or treatment known in the art that imitates the effects of radiation. As would be appreciated by the skilled artisan, chemotherapy includes the administration of a therapeutically effective amount of at least one chemotherapeutic agent. In some aspects, the at least one chemotherapeutic agent may include, but it is not limited to, Actinomycin, All-trans retinoic acid, Azacitidine, Azathioprine, Bleomycin, Bortezomib, Carboplatin, Capecitabine, Cisplatin, Chlorambucil, Cyclophosphamide, Cytarabine, Daunorubicin, Docetaxel, Doxifluridine, Doxorubicin, Epirubicin, Epothilone, Etoposide, Fluorouracil, Gemcitabine, Hydroxyurea, Idarubicin, Imatinib, Irinotecan, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitoxantrone, Oxaliplatin, Paclitaxel, Pemetrexed, Teniposide, Tioguanine, Topotecan, Valrubicin, Vemurafenib, Vinblastine, Vincristine, Vindesine. In some aspects, the at least one chemotherapeutic agent comprises Cytarabine. In some aspects, the at least one chemotherapeutic agent comprises Melphalan.

[0067] As used herein, the term "treating" or "treat" describes the management and care of a subject for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model.

[0068] It is to be appreciated that references to "treating" or "treatment" include the alleviation of established symptoms of a condition. As used herein, "treating" or "treatment" of a state, disorder or condition therefore includes: (1) delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed

to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, *i.e.*, arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, *i.e.*, causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0069] As used herein, the term "preventing," "prevent," or "protecting against" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0070] The term "therapeutically effective amount", as used herein, refers to an amount of a pharmaceutical agent, *e.g.*, apraglutide, to treat, or prevent an identified disease or condition, *e.g.*, GvHD, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0071] For any compound, the therapeutically effective amount can be estimated in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}. The dosage may vary within this range depending upon the dosage form employed and sensitivity of the subject.

[0072] The terms "administer", "administering", "administration", and the like, as used herein, refer to methods that may be used to enable delivery of compositions to the desired site of biological action. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous, orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like. Administration techniques that can be employed with the agents and methods described herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.;

Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

[0073] In addition, the apraglutide can be co-administered with other therapeutic agents. As used herein, the terms "co-administration", "administered in combination with", and their grammatical equivalents, are meant to encompass administration of two or more therapeutic agents to a single subject, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. In some aspects, apraglutide will be co-administered with other agents. These terms encompass administration of two or more agents to the subject so that both agents and/or their metabolites are present in the subject at the same time. They include simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present (*i.e.*, co-formulation). Thus, the compounds described herein and the other agent(s) may be administered in a single composition.

[0074] In some aspects, the present disclosure provides a method of treating or preventing GvHD in a subject, the method comprising administering to the subject at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a method of treating GvHD in a subject, the method comprising administering to the subject at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a method of preventing GvHD in a subject, the method comprising administering to the subject at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof.

[0075] In some aspects, the present disclosure provides a method of treating or preventing GvHD in a subject, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a method of treating GvHD in a subject, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a method of preventing GvHD in a subject, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof.

[0076] In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of GvHD in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount.

[0077] In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of GvHD in a subject. In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment of GvHD in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount. In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment of GvHD in a subject. In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, is for use in the prevention of GvHD in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount. In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in the prevention of GvHD in a subject.

[0078] In some aspects, the present disclosure provides the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing GvHD in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount.

[0079] In some aspects, the present disclosure provides the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing GvHD in a subject. In some aspects, the present disclosure provides the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating GvHD in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount. In some aspects, the present disclosure provides the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating GvHD in a subject. In some aspects, the present disclosure provides the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for preventing GvHD in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount. In some aspects, the present disclosure provides the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for preventing GvHD in a subject.

[0080] Also provided herein are suitable therapeutically effective amounts in which apraglutide, or a pharmaceutically acceptable salt thereof, can be used or administered to a subject for treating or preventing GvHD. In some aspects, the present disclosure provides a method of treating GvHD-induced intestinal damage in a subject who has been previously

diagnosed with GvHD, the method comprising administering to the subject at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a method of treating GvHD-induced intestinal damage in a subject who has been previously diagnosed with GvHD, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD is ongoing at the time of the administration of apraglutide. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD has been successfully treated prior to the administration of apraglutide. In some aspects, the subject is expected to undergo a transplant.

[0081] In some aspects of the methods and uses described herein, the subject is older than 65 years. In some aspects, the subject is between 18 and 64 years old. In some aspects, the subject is younger than 18 years old.

[0082] In some aspects of the methods and uses described herein, the subject weighs more than 50 kg. In some aspects, the subject weighs between 50 kg and 40 kg. In some aspects, the subject weighs less than 40 kg. In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in treating GvHD-induced intestinal damage in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount. In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in treating GvHD-induced intestinal damage in a subject. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD is ongoing at the time of the administration of apraglutide. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD has been successfully treated prior to the administration of apraglutide.

[0083] In some aspects, the present disclosure provides the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating GvHD-induced intestinal damage in a subject, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides, in part, the use of apraglutide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating GvHD-induced intestinal damage in a subject. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD is ongoing at the time of the administration of apraglutide. In some aspects, the subject has been previously diagnosed with GvHD, and the GvHD has been successfully treated prior to the administration of apraglutide.

[0084] In some aspects, the GvHD-induced intestinal damage can include, but is not limited to, malabsorption, diarrhea, abdominal pain, mucositis, mucosal ulceration, nausea, shortening of the colon, shortening of the small intestine and any other GvHD-induced gastrointestinal complication known in the art.

[0085] In some aspects of the methods and uses of the present disclosure, the GvHD can be acute GvHD. In some aspects, the acute GvHD can be late acute GvHD. In some aspects, the acute GvHD is acute gastrointestinal GvHD.

[0086] In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-refractory GvHD. In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-naïve GvHD.

[0087] In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-refractory acute GvHD. In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-naïve acute GvHD.

[0088] In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-refractory acute gastrointestinal GvHD. In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-naïve acute gastrointestinal GvHD.

[0089] In some embodiments of the present disclosure, the GvHD can be acute GvHD, such as late acute GvHD. The acute GvHD may be steroid-naive acute GvHD. Alternatively, the acute GvHD may be steroid-refractory acute GvHD. The acute GvHD may be acute gastrointestinal GvHD, such as steroid-refractory acute gastrointestinal GvHD. For example, apraglutide, or a pharmaceutically acceptable salt thereof, may be for use in the prevention of acute GvHD, such as gastrointestinal GvHD, in a subject. For example, apraglutide, or a pharmaceutically acceptable salt thereof, may be for use in the treatment of steroid-refractory acute GvHD, such as steroid-refractory acute gastrointestinal GvHD, in a subject.

[0090] In some aspects of the methods and uses of the present disclosure, the GvHD can be chronic GvHD.

[0091] In some aspects of the methods and uses of the present disclosure, chronic GvHD can be chronic gastrointestinal GvHD. In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-refractory chronic gastrointestinal GvHD. In some aspects of the methods and uses of the present disclosure, the GvHD can be steroid-naïve chronic gastrointestinal GvHD.

[0092] In some aspects of the present disclosure, the GvHD can be chronic GvHD, such as late chronic GvHD. The chronic GvHD may be steroid-naive chronic GvHD. Alternatively, the chronic GvHD may be steroid-refractory chronic GvHD. The chronic GvHD may be chronic

gastrointestinal GvHD, such as steroid-refractory chronic gastrointestinal GvHD. For example, apraglutide, or a pharmaceutically acceptable salt thereof, may be for use in the prevention of chronic GvHD, such as gastrointestinal GvHD, in a subject. For example, apraglutide, or a pharmaceutically acceptable salt thereof, may be for use in the treatment of steroid-refractory chronic GvHD, such as steroid-refractory chronic gastrointestinal GvHD, in a subject.

[0093] In some aspects of the methods and uses of the present disclosure, the GvHD can be Overlap Syndrome.

[0094] In some aspects of the methods and uses of the present disclosure, a subject has grade II- IV GvHD according to the Mount Sinai Acute Graft Versus Host Disease International Consortium (MAGIC) scale. In some aspects, the subject has grade III-IV GvHD according to the MAGIC scale. In some aspects, the subject has grade II-III GvHD according to the MAGIC scale. In some aspects, the subject has grade II, III or IV GvHD according to the MAGIC scale.

[0095] Target organ staging on the MAGIC Grading Scale is provided in **Table 1** below. Overall clinical grade based on the most severe target organ involvement is provided in **Table 2**.

Table 1. MAGIC Grading Scale for Target Organ Staging

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (Stool Output/Day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	<500 mL/day or <3/episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	500-999 mL/day or 3-4 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		1000-1500 mL/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		>1500 mL/day or >7/episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

BSA= body surface area; GI=gastrointestinal tract; GVHD=graft versus host disease

Table 2. MAGIC Grading Scale for Overall Clinical Grade

Based on the most severe target organ involvement

Grade	Description
0	No Stage 1-4 of any organ
I	Stage 1-2 skin without liver, upper GI or lower GI involvement
II	Stage 3 rash and/or Stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI
III	Stage 2-3 liver and/or Stage 2-3 lower GI, with Stage 0-3 skin and/or Stage 0-1 upper GI
IV	Stage 4 skin, liver, or lower GI involvement, with Stage 0-1 upper GI

GI = gastrointestinal tract

[0096] In some aspects of the methods and uses of the present disclosure, the GvHD is upper gut or upper gastrointestinal (GI) Graft versus Host Disease.

[0097] In some aspects of the methods and uses of the present disclosure, the GvHD is mid-lower gut or mid-lower gastrointestinal (GI) Graft versus Host Disease.

[0098] In some aspects of the methods and uses of the present disclosure, the subject has stage 1-4 GvHD for the lower GI at baseline. As used herein, "baseline" refers to the MAGIC stage at day 0 of treatment, *i.e.*, prior to apraglutide administration.

[0099] In some aspects, when the baseline is stage 1-4 GvHD according to the MAGIC scale for lower GI, after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased to stage 0. In some aspects, the decrease to stage 0 is maintained through at least day 90, *e.g.*, at least day 120, at least day 150, at least 6 months, at least 1 year, or at least 2 years.

[00100] In some aspects, when the baseline is stage 1-4 GvHD according to the MAGIC scale for all organs, after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased to stage 0. In some aspects, the decrease to stage 0 is maintained through at least day 90, *e.g.*, at least day 120, at least day 150, at least 6 months, at least 1 year, or at least 2 years.

[00101] As used herein, a subject who displays a decrease to stage 0 according to the MAGIC scale for lower GI is a "complete responder" or displays a "complete response" for lower GI. As used herein, a subject who displays a decrease to stage 0 according to the MAGIC scale for all-organs is a "complete responder" or displays a "complete response."

[00102] In some aspects, when the baseline is stage 1-4 GvHD according to the MAGIC scale for lower GI, after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased by at least one stage. In some aspects, the decrease of at least

one stage is maintained through at least day 90, *e.g.*, at least day 120, at least day 150, at least 6 months, at least 1 year, or at least 2 years.

[00103] In some aspects, when the baseline is stage 1-4 GvHD according to the MAGIC scale for all organs, after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased by at least one stage. In some aspects, the decrease of at least one stage is maintained through at least day 90, *e.g.*, at least day 120, at least day 150, at least 6 months, at least 1 year, or at least 2 years.

[00104] As used herein, a subject who displays a decrease of at least 1 stage compared to baseline according to the MAGIC scale for lower GI is a "partial responder" or displays a "partial response" for lower GI. As used herein, a subject who displays a decrease of at least 1 stage in any organ according to the MAGIC scale without worsening of another organ compared to baseline is a "partial responder" or displays a "partial response" for all organs.

[00105] In some aspects of the present disclosure, the GvHD can be liver GvHD. In some aspects of the methods and uses of the present disclosure, the GvHD is liver GvHD. For example, apraglutide, or a pharmaceutically acceptable salt thereof, may be for use in the prevention or treatment of liver GvHD in a subject.

[00106] In some aspects of the methods and uses of the present disclosure, the subject has a cancer. In some aspects, the cancer is a hematological cancer. In some aspects, the cancer is at least one of acute myeloid leukemia, myelodysplastic syndrome, follicular lymphoma, diffuse large B cell lymphoma, acute lymphoblastic leukemia, multiple myeloma, Hodgkin lymphoma, chronic myeloid leukemia, T cell non-Hodgkin lymphoma, lymphoblastic B cell non-Hodgkin lymphoma (non-Burkitt), Burkitt's lymphoma, anaplastic large cell lymphoma, germ cell tumor, Ewing's sarcoma, soft tissue sarcoma, neuroblastoma, Wilms' tumor, osteosarcoma, medulloblastoma, acute promyelocytic leukemia, mantle cell lymphoma, T cell lymphoma, lymphoplasmacytic lymphoma, cutaneous T cell lymphoma, plasmablastic lymphoma, chronic lymphocytic leukemia, breast cancer and renal cancer.

[00107] In some aspects of the present disclosure, the subject has a cancer. The cancer may be a hematological cancer. The cancer can be at least one of Acute myeloid leukemia, myelodysplastic syndrome, follicular lymphoma, diffuse large B cell lymphoma, acute lymphoblastic leukemia, multiple myeloma, Hodgkin lymphoma, chronic myeloid leukemia, T cell non-Hodgkin lymphoma, lymphoblastic B cell non-Hodgkin lymphoma (non-Burkitt), Burkitt's lymphoma, anaplastic large cell lymphoma, germ cell tumor, Ewing's sarcoma, soft tissue sarcoma, neuroblastoma, Wilms' tumor, osteosarcoma, medulloblastoma, acute promyelocytic leukemia, mantle cell lymphoma, T cell lymphoma, lymphoplasmacytic

lymphoma, cutaneous T cell lymphoma, plasmablastic lymphoma, chronic lymphocytic leukemia, breast cancer and renal cancer. For example, the subject can be diagnosed with a cancer and be designated to undergo an allogeneic transplant. Alternatively, the subject can be diagnosed with a cancer and has previously undergone an autologous transplant. Alternatively, the subject can be diagnosed with a cancer and has previously undergone an allogeneic transplant. Alternatively, the subject can be diagnosed with a cancer and has previously undergone an autologous transplant. In some aspects, the transplant is in a subject having, for example, myelofibrosis. In some aspects, the transplant is an autologous transplant in a subject having multiple myeloma.

[00108] In some aspects of the methods and uses of the present disclosure, a subject has a disease or disorder, *e.g.*, a disease or disorder requiring a transplant. In some aspects, the disease or disorder can be at least one of a hemoglobinopathy, a congenital hemoglobinopathy, β-Thalessemia major (TM), sickle cell disease (SCD), severe aplastic anemia, Fanconi's anemia, dyskeratosis congenita, Blackfan-Diamond anemia, Thalassemia, congenital amegakaryocytic thrombocytopenia, severe combined immunodeficiency, T cell immunodeficiency, T cell immunodeficiency-SCID variants, Wiskott-Aldrich syndrome, a hemophagocytic disorder, a lymphoproliferative disorder, severe congenital neutropenia, chronic granulomatous disease, a phagocytic cell disorder, IPEX syndrome, juvenile rheumatoid arthritis, systemic sclerosis, an autoimmune disorder, an immune dysregulation disorder, mucopolysaccharoidoses, MPS-I, MPS-VI, osteopetrosis, a metabolic disease, globoid cell leukodystrophy (Krabbe), metachromatic leukodystrophy, cerebral X-linked adrenoleukodystrophy, a myelofibrosis disease, a myeloproliferative disease, a plasma cell disorder, a mast cell disease, common variable immunodeficiency, chronic granulomatous disease, multiple sclerosis, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease and polymyositis-dermatomyositis.

[00109] In some aspects of the present disclosure, a subject has a disease or disorder, *e.g.*, a disease or disorder requiring a transplant. The disease or disorder may be at least one of a hemoglobinopathy, a congenital hemoglobinopathy, β-Thalessemia major (TM), sickle cell disease (SCD), severe aplastic anemia, Fanconi's anemia, dyskeratosis congenita, Blackfan-Diamond anemia, Thalassemia, congenital amegakaryocytic thrombocytopenia, severe combined immunodeficiency, T cell immunodeficiency, T cell immunodeficiency-SCID variants, Wiskott-Aldrich syndrome, a hemophagocytic disorder, a lymphoproliferative disorder, severe congenital neutropenia, chronic granulomatous disease, a phagocytic cell disorder, IPEX syndrome, juvenile rheumatoid arthritis, systemic sclerosis, an autoimmune

disorder, an immune dysregulation disorder, mucopolysaccharoidoses, MPS-I, MPS-VI, osteopetrosis, a metabolic disease, globoid cell leukodystrophy (Krabbe), metachromatic leukodystrophy, cerebral X-linked adrenoleukodystrophy, a myelofibrosis disease, a myeloproliferative disease, a plasma cell disorder, a mast cell disease, common variable immunodeficiency, chronic granulomatous disease, multiple sclerosis, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease and polymyositis-dermatomyositis. For example, the subject can be diagnosed with a disease or disorder and be designated to undergo an allogeneic transplant. For example, the subject can be diagnosed with a disease or disorder and be designated to undergo an autologous transplant. Alternatively, the subject can be diagnosed with a disease or disorder and has previously undergone an allogeneic transplant. Alternatively, the subject can be diagnosed with a disease or disorder and has previously undergone an autologous transplant.

[00110] In some aspects of the methods and uses of the present disclosure, a subject has a cancer and is designated to undergo a transplant in order to treat the cancer. In some aspects of the methods and uses of the present disclosure, a subject has a cancer and has previously undergone a transplant in order to treat the cancer.

[00111] In some aspects of the methods and uses of the present disclosure, a subject has a cancer and is designated to undergo an allogeneic transplant in order to treat the cancer. In some aspects of the methods and uses of the present disclosure, a subject has a cancer and has previously undergone an allogeneic transplant in order to treat the cancer.

[00112] In some aspects of the methods and uses of the present disclosure, a subject has a cancer and is designated to undergo an autologous transplant in order to treat the cancer. In some aspects of the methods and uses of the present disclosure, a subject has a cancer and has previously undergone an autologous transplant in order to treat the cancer.

[00113] In some aspects of the methods and uses of the present disclosure, a subject has a disease or disorder and is designated to undergo a transplant in order to treat the disease or disorder. In some aspects of the methods and uses of the present disclosure, a subject has a disease or disorder and has previously undergone a transplant in order to treat the disease or disorder.

[00114] In some aspects of the methods and uses of the present disclosure, a subject has a disease or disorder and is designated to undergo an allogeneic transplant in order to treat the disease or disorder. In some aspects of the methods and uses of the present disclosure, a subject has a disease or disorder and has previously undergone an allogeneic transplant in order to treat the disease or disorder.

[00115] In some aspects of the methods and uses of the present disclosure, a subject has a disease or disorder and is designated to undergo an autologous transplant in order to treat the disease or disorder. In some aspects of the methods and uses of the present disclosure, a subject has a disease or disorder and has previously undergone an autologous transplant in order to treat the disease or disorder.

[00116] In some aspects of the methods and uses of the present disclosure, a subject has been previously administered a transplant. Accordingly, in some aspects, at least one therapeutically effective amount of apraglutide can be administered to the subject after the subject has been administered a transplant.

[00117] In some aspects of the present disclosure, a subject has been previously administered a transplant. Accordingly, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject after the latter has been administered a transplant.

[00118] In some aspects of the methods and uses of the present disclosure, a subject has been previously administered an allogeneic transplant. Accordingly, in some aspects, at least one therapeutically effective amount of apraglutide is administered to the subject after the subject has been administered an allogeneic transplant.

[00119] In some aspects of the present disclosure, a subject has been previously administered an allogeneic transplant. Accordingly, apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered an allogeneic transplant.

[00120] In some aspects of the methods and uses of the present disclosure, a subject has been previously administered an autologous transplant. Accordingly, in some aspects, at least one therapeutically effective amount of apraglutide is administered to the subject after the subject has been administered an autologous transplant.

[00121] In some aspects of the present disclosure, a subject can have been previously administered an autologous transplant. Accordingly, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject after the subject has been administered an autologous transplant.

[00122] In some aspects of the methods and uses of the present disclosure, a subject has been previously administered a conditioning therapy in connection with a transplant. In some aspects of the methods and uses of the present disclosure, a subject has been previously administered a conditioning therapy in connection with an allogeneic transplant. In some aspects of the methods and uses of the present disclosure, a subject has been previously administered a conditioning therapy in connection with an autologous transplant. In some

aspects, a conditioning therapy can comprise the administration of radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof. In some aspects, a radiation therapy can comprise total body irradiation.

[00123] A conditioning therapy may be administered in connection with the allogenic transplant. A conditioning therapy can comprise, consist essentially of, or consist of, the administration of radiation therapy, chemotherapy, radiomimetic therapy, or any combination thereof. In some embodiments, the conditioning therapy comprises radiation therapy. The radiation therapy can comprise total body irradiation. In some embodiments, the conditioning therapy comprises chemotherapy. In some embodiments, the conditioning therapy comprises radiomimetic therapy.

[00124] Accordingly, in some aspects, at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered a conditioning therapy in connection with a transplant. In some aspects, at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject after the subject has been administered a conditioning therapy in connection with an allogeneic transplant. In some aspects, at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject after the subject has been administered a conditioning therapy in connection with an autologous transplant. In some aspects, at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject after the subject has been administered a radiation therapy, chemotherapy radiomimetic therapy or any combination thereof.

[00125] Accordingly, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject after the subject has been administered a conditioning therapy in connection with a transplant. Accordingly, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject after the subject has been administered a conditioning therapy in connection with an allogeneic transplant. Accordingly, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject after the subject has been administered a conditioning therapy in connection with an autologous transplant.

[00126] In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject prior to the subject being administered a transplant. In some aspects of the methods and uses of the present disclosure, at least one therapeutically

effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered prior the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with the transplant. In some aspects of the methods and uses of the present disclosure, at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof and prior to the subject being administered a transplant.

[00127] In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject prior to the subject being administered a transplant. In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered prior the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with the transplant. In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof and prior to the subject being administered a transplant.

[00128] In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject prior to the subject being administered a solid organ transplant. In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered prior the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with the solid organ transplant. In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof and prior to the subject being administered a solid organ transplant.

[00129] In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject prior to the subject being administered an allogeneic transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered prior the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with the allogeneic transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of

apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof and prior to the subject being administered an allogeneic transplant.

[00130] In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject prior to the subject being administered an allogeneic transplant. In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered prior the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with the allogeneic transplant. In some aspects of the methods and uses of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof and prior to the subject being administered an allogeneic transplant.

[00131] In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject prior to the subject being administered an autologous transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered prior the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with the autologous transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof and prior to the subject being administered an autologous transplant.

[00132] In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject prior to the subject being administered an autologous transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered prior the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with the autologous transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, is administered to the subject after

the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof and prior to the subject being administered an autologous transplant.

[00133] In some aspects of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject prior to the subject being administered an allogeneic transplant. For example, administration of apraglutide, or a pharmaceutically acceptable salt thereof, can be prior the subject being administered radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof in connection with the allogeneic transplant or after the subject has been administered radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof but prior to the subject being administered an allogeneic transplant.

[00134] In some aspects of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject prior to the subject being administered an autologous transplant. For example, administration of apraglutide, or a pharmaceutically acceptable salt thereof, can be prior the subject being administered radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof in connection with the autologous transplant or after the subject has been administered radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof but prior to the subject being administered an autologous transplant.

[00135] In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject concurrently with a transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject concurrently with an allogeneic transplant. In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject concurrently with an autologous transplant.

[00136] In some aspects of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject concurrently with a transplant. In some aspects of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject concurrently with an allogeneic transplant. In some aspects of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject concurrently with an autologous transplant.

[00137] In some aspects of the methods and uses of the present disclosure, an at least one therapeutically effective amount of apraglutide can be administered to a subject concurrently with a conditioning therapy. In some aspects, an at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to a subject concurrently with a radiation therapy, a chemotherapy, a radiomimetic therapy, or any combination thereof.

[00138] In some aspects of the present disclosure, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered to the subject concurrently with a conditioning therapy, such as a conditioning therapy as defined above.

[00139] In some aspects of the methods and uses of the present disclosure, a subject can have been previously diagnosed with GvHD and undergone a preliminary GvHD treatment. In some aspects, the preliminary GvHD treatment can comprise the administration of an anti-GvHD treatment. In some aspects, an anti-GvHD treatment can comprise the administration a steroid therapy. Accordingly, in some aspects of the methods and uses of the present disclosure, a subject can have been previously administered steroid therapy. As would be appreciated by the skilled artisan, steroid therapy can comprise the administration of at least one corticosteroid. As would be appreciated by the skilled artisan, steroid therapy can comprise the administration of prednisone, methylprednisolone, dexamethasone, beclomethasone, budesonide or any combination thereof.

[00140] In some aspects of the methods and uses of the present disclosure, administration of apraglutide, or a pharmaceutically acceptable salt thereof, can prevent and/or attenuate a reduction in colon length in a subject following an allogeneic transplant. In some aspects, administration of apraglutide, or a pharmaceutically acceptable salt thereof, prevents and/or attenuates a reduction in colon length in a subject following a conditioning therapy and a transplant. In some aspects, administration of apraglutide, or a pharmaceutically acceptable salt thereof, prevents and/or attenuates a reduction in colon length in a subject following a conditioning therapy and an allogeneic transplant. In some aspects, administration of apraglutide, or a pharmaceutically acceptable salt thereof, prevents and/or attenuates a reduction in colon length in a subject following a conditioning therapy and an autologous transplant.

[00141] Without wishing to be bound by theory, it is hypothesized that the administration of apraglutide, or a pharmaceutically acceptable salt thereof, can prevent and/or attenuate a reduction in colon length in a subject following a transplant. The administration of apraglutide, or a pharmaceutically acceptable salt thereof, may prevent and/or attenuate a

reduction in colon length in a subject following a conditioning therapy and an allogeneic transplant. The administration of apraglutide, or a pharmaceutically acceptable salt thereof, can prevent and/or attenuate a reduction in colon length in a subject following an allogeneic transplant. The administration of apraglutide, or a pharmaceutically acceptable salt thereof, may prevent and/or attenuate a reduction in colon length in a subject following a conditioning therapy and an autologous transplant.

[00142] The administration of apraglutide, or a pharmaceutically acceptable salt thereof, can further stabilize the intestinal microbiota.

[00143] In some aspects, the present disclosure provides a method of treating GvHD-induced intestinal damage in a subject who has been previously diagnosed with GvHD, the method comprising administering to the subject at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, concurrently with a immunosuppressive therapy, *e.g.*, ruxolitinib. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD is ongoing at the time of the administration of apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD has been successfully treated prior to the administration of apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a method of treating GvHD-induced intestinal damage in a subject, the method comprising administering to the subject a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of an immunosuppressive therapy. In some aspects, the treatment further comprises a systemic steroid. In some aspects, the present disclosure provides a method of treating GvHD-induced intestinal damage in a subject, the method comprising administering to the subject a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of a calcineurin inhibitor.

[00144] In some aspects, the present disclosure provides a method of treating GvHD-induced intestinal damage in a subject who has been previously diagnosed with GvHD, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof, concurrently with a immunosuppressive therapy, *e.g.*, ruxolitinib. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD is ongoing at the time of the administration of apraglutide. In some aspects, the subject has been previously diagnosed with GvHD and the GvHD has been successfully treated prior to the administration of apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present

disclosure provides a method of treating GvHD-induced intestinal damage in a subject, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of an immunosuppressive therapy. In some aspects, the treatment further comprises a systemic steroid. In some aspects, the present disclosure provides a method of treating GvHD-induced intestinal damage in a subject, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of a calcineurin inhibitor.

[00145] In some aspects, the present disclosure provides a method of treating cancer comprising administering to a subject a combination of apraglutide, or a pharmaceutically acceptable salt thereof, and at least one chemotherapy. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00146] In some aspects, the administration of apraglutide, or a pharmaceutically acceptable salt thereof, can treat chemotherapy-induced intestinal damage in a subject. Accordingly, the present disclosure provides, in part, a method of treating chemotherapy-induced intestinal damage in a subject in need thereof, the method comprising administering to the subject at least one therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides a method of treating chemotherapy-induced intestinal damage in a subject in need thereof, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof. In some aspects, the present disclosure provides apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment of chemotherapy-induced intestinal damage in a subject. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00147] In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of a conditioning therapy. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject apraglutide, or a pharmaceutically acceptable salt thereof, prior to, concurrent with, or after administration of a therapeutically effective amount of a conditioning therapy. In some aspects, of the disclosure, the conditioning therapy is, for example, chemotherapy. In some aspects, the treatment further comprises an

immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid. In some aspects, the chemotherapy comprises a combination therapy.

[00148] In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and b) a transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a conditioning therapy; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) a transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof,; and c) a transplant.

[00149] In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) apraglutide, or a pharmaceutically acceptable salt thereof; and b) a transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a conditioning therapy; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) a transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) a transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00150] In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and b) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a conditioning therapy; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) a therapeutically effective

amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00151] In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) apraglutide, or a pharmaceutically acceptable salt thereof; and b) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) conditioning therapy; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00152] In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and b) an autologous transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a conditioning therapy; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00153] In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) apraglutide, or a pharmaceutically acceptable salt thereof; and b) an autologous transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject: a) conditioning therapy; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the

subject: a) radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00154] It is contemplated herein that the presently disclosed effect of apraglutide on GvHD can be useful in the context of an anticancer therapy. GvHD developing in this context can also be referred to as anticancer therapy-related GvHD. For example, and without limitation, a typical anticancer therapy that can benefit from the presently disclosed effect of apraglutide is one that includes the administration of an allogeneic or autologous transplant to a subject, such as the administration of a conditioning therapy and the subsequent administration of an allogeneic or autologous transplant. In this context, it may be advantageous to further administer apraglutide, or a pharmaceutically acceptable salt thereof. For example, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered before the administration of an allogeneic or autologous transplant, such between the administration of a conditioning therapy and the administration of an allogeneic or autologous transplant to a subject.

[00155] Accordingly, the present disclosure provides, in part, apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of anticancer therapy-related GvHD in a subject.

[00156] In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and b) a transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a conditioning therapy; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) a transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) a transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00157] In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) apraglutide, or

a pharmaceutically acceptable salt thereof; and b) a transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a conditioning therapy; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) a transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) a transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00158] In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and b) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a conditioning therapy; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00159] In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) apraglutide, or a pharmaceutically acceptable salt thereof; and b) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) conditioning therapy; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an allogeneic transplant. In some aspects, the treatment further comprises an

immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00160] In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and b) an autologous transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a conditioning therapy; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) a therapeutically effective amount of a radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) a therapeutically effective amount of apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00161] In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) apraglutide, or a pharmaceutically acceptable salt thereof; and b) an autologous transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) conditioning therapy; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject: a) radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof; b) apraglutide, or a pharmaceutically acceptable salt thereof; and c) an autologous transplant. In some aspects, the treatment further comprises an immunosuppressant, *e.g.*, ruxolitinib. In some aspects, the treatment further comprises a systemic steroid.

[00162] In any of the methods or uses described herein, reference to apraglutide also encompasses a pharmaceutically acceptable salt of apraglutide. In some aspects, the pharmaceutically acceptable salt of apraglutide is a sodium salt of apraglutide.

[00163] In some aspects of the methods or uses described herein, a subject has been previously administered an immunosuppressant, *e.g.*, ruxolitinib prior to the administration of apraglutide, or a pharmaceutically acceptable salt thereof.

[00164] In any of the methods or uses described here, apraglutide, or a pharmaceutically acceptable salt thereof, can be administered in combination with at least one second active agent. In some aspects, the at least one second active agent can be ruxolitinib. In some aspects, the at least one second active agent can be a calcineurin inhibitor. In some aspects, the at least one second active agent can be a systemic steroid.

[00165] In some aspects, the subject initiates ruxolitinib treatment no more than 72 hours (*e.g.*, less than 3 days, less than 2 days, or less than 1 day) prior to initiating apraglutide treatment. In some embodiments, the subject initiates ruxolitinib treatment concurrently with initiating apraglutide treatment.

[00166] Administration of ruxlotinib alone can provide a complete or partial response to day 28 of treatment, as shown for example in Zeiser *et al.*, (2020) *NEJM*, 382:1800-1810.

[00167] In some aspects, administration of apraglutide, or a pharmaceutically acceptable salt thereof, maintains a decreased MAGIC lower GI stage for at least about 3× as many days as a subject administered ruxolitinib only. In some embodiments, administration of apraglutide maintains the decreased MAGIC stage for at least 4× as many days, at least 5× as many days, at least 6× as many days, at least 7× as many days, at least 8× as many days, at least 9× as many days, or at least 10× as many days as a subject administered ruxolitinib only.

[00168] In some aspects, administration of apraglutide or a pharmaceutically salt thereof concurrently with ruxolitinib decreases relapse compared to a subject administered ruxolitinib only.

[00169] In some aspects, administration of apraglutide or a pharmaceutically acceptable salt thereof concurrently with ruxolitinib decreases mortality compared to a subject administered ruxolitinib only.

[00170] In some aspects, administration of apraglutide or a pharmaceutically acceptable salt thereof concurrently with ruxolitinib decreases the non-relapse mortality compared to a subject administered ruxolitinib only. As used herein, "non-relapse mortality" refers to a death that was not preceded by a relapse or progression of the malignancy or disease which necessitated the transplant.

[00171] In some aspects, administration of apraglutide or a pharmaceutically acceptable salt thereof concurrently with ruxolitinib increases overall survival compared to a subject administered ruxolitinib only.

[00172] In some aspects of the methods and uses described herein, apraglutide, or a pharmaceutically acceptable salt thereof can be administered in temporal proximity with

another therapeutic intervention described herein (*e.g.*, a transplant, a conditioning therapy, chemotherapy, a second active agent, *etc.*).

[00173] In some aspects of the methods and uses of the present disclosure, a transplant can comprise hematopoietic stem cells. In some aspects, the hematopoietic stem cells can be derived from bone marrow, peripheral blood, umbilical cord blood or any combination thereof. In some aspects, of the methods and uses of the present disclosure, a transplant can be an allogeneic transplant or an autologous transplant.

[00174] In some aspects of the methods and uses of the present disclosure, an allogeneic transplant can comprise allogeneic hematopoietic stem cells. In some aspects, the allogeneic hematopoietic stem cells can be derived from bone marrow, peripheral blood, umbilical cord blood or any combination thereof.

[00175] In some aspects of the methods and uses of the present disclosure, an autologous transplant can comprise autologous hematopoietic stem cells. In some aspects, the autologous hematopoietic stem cells can be derived from bone marrow, peripheral blood, umbilical cord blood or any combination thereof.

[00176] In some aspects of the methods and uses of the present disclosure, a transplant can comprise T-cells. In some aspects, T-cells can be chimeric antigen receptor (CAR) T-cells.

[00177] In some aspects of the methods and uses of the present disclosure, an allogeneic transplant can comprise allogeneic T-cells. In some aspects, allogeneic T-cells can be allogenic chimeric antigen receptor (CAR) T-cells. In some aspects of the methods and uses of the present disclosure, an autologous transplant can comprise autologous T-cells. In some aspects, autologous T-cells can be autologous chimeric antigen receptor (CAR) T-cells.

[00178] In some aspects of the present disclosure, an allogeneic transplant can comprise the transplant of allogeneic hematopoietic stem cells. The allogeneic hematopoietic stem cells can be derived from bone marrow, peripheral blood, umbilical cord blood or any combination thereof.

[00179] In some aspects of the present disclosure, an allogeneic transplant can comprise the transplant of allogeneic T-cells. Allogeneic T-cells can be allogenic chimeric antigen receptor (CAR) T-cells.

[00180] In some aspects of the present disclosure, an autologous transplant can comprise the transplant of autologous hematopoietic stem cells. The autologous hematopoietic stem cells can be derived from bone marrow, peripheral blood, umbilical cord blood or any combination thereof.

[00181] In some aspects of the present disclosure, an autologous transplant can comprise the transplant of autologous T-cells. Autologous T-cells can be allogenic chimeric antigen receptor (CAR) T-cells.

Dosing and Administration

[00182] In some aspects, the apraglutide is administered parenterally. The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (*e.g.*, the subject, the disease, the disease state involved, the particular treatment). Treatment can involve daily or multi-daily or less than daily (such as weekly or monthly, *etc.*) doses over a period of a few days to months, or even years. However, a person of ordinary skill in the art would readily appreciate appropriate and/or equivalent doses looking at dosages of apraglutide used in the treatment of other diseases and conditions, including, but not limited to, short bowel syndrome.

[00183] Weights for apraglutide in a dosage or a formulation listed herein are given for the amount of apraglutide without any salt appendages. For example, when apraglutide is in the sodium salt form, only the weight of apraglutide without the sodium counterions is taken into account when listing the weight of apraglutide in a dosage or a formulation. In some embodiments, the content of apraglutide without any counterions in a sample can be measured by reverse phase ultra performance liquid chromatography using an external reference standard for apraglutide.

[00184] Without wishing to be bound by theory, it is believed that due to the non-linear increase of exposures (AUC and C_{max}) as body weight decreases, it is desired to dose patients with body weight below 50 kg with, for example, 1.5 mg apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, to prevent high exposures. Patients of 50 kg or higher may receive 3.6 mg doses of apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof.

[00185] Doses generally range from about 1 mg to about 10 mg per week for a period of about 1 week to about 100 weeks. In some aspects, the weekly dose is between about 1 mg and 10 mg. In some aspects, subjects are dosed from between about 1 weeks to about 100 weeks, about 1 weeks to about 80 weeks, about 1 weeks to about 60 weeks, about 1 weeks to about 48 weeks, about 1 weeks to about 26 weeks, about 1 weeks to about 13 weeks, about 1 weeks to about 8 weeks, about 2 weeks to about 24 weeks, about 2 weeks to about 20 weeks, or about 2 weeks to about 16 weeks. In some aspects, subjects may be administered a weekly dose range from about 1 mg to about 30 mg. In some aspects, subjects may be administered a

weekly dose range from about 1 mg to about 28.4 mg. In some aspects, subjects may be administered a once a week of about 10 mg. In some aspects, subjects may be administered a once a week of about 5 mg. In some aspects, subjects may be administered a once a week of about 2.5 mg. In some aspects, subjects may be administered a once a week of about 1 mg. For example, subjects may be administered a dose about once a week. Subjects may be administered a dose about once every two weeks or about twice a month. About once every two weeks or about twice a month. Patients with a body weight below 50 kg can be administered apraglutide in an amount of 2.5 mg to prevent high exposures. In some aspects, patients with a body weight of 50 kg or greater can be administered apraglutide in an amount of 5 mg or more. In some embodiments: the subject has a body weight of 50 kg or greater, and apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a dose of about 3.6 mg; or the subject has a body weight less than 50 kg, and the apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a dose of about 1.5 mg.

[00186] In some aspects, the subject has a body weight less than 50 kg, and the apraglutide or a pharmaceutically acceptable salt thereof, e.g., the sodium salt thereof, is administered at a dose of 1.5±1.0 mg, 1.5±0.9 mg, 1.5±0.8 mg, 1.5±0.7 mg, 1.5±0.6 mg, 1.5±0.5 mg, 1.5±0.4 mg, 1.5±0.3 mg, 1.5±0.2 mg, or 1.5±0.1 mg (*e.g.*, about 1.5 mg).

[00187] In some aspects, the subject has body weight less than 50 kg, and the apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a weekly dose of about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1.0 mg, about 1.1 mg, about 1.2 mg, about 1.3 mg, about 1.4 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 2.0 mg, about 2.1 mg, about 2.2 mg, about 2.3 mg, about 2.4 mg, or about 2.5 mg.

[00188] In some aspects, the subject has a body weight less than 50 kg, and the apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a dose of about 1.5 mg.

[00189] In some aspects, the subject has a body weight of 50 kg to 60 kg, and the apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a dose of 3.6±1.0 mg, 3.6±0.9 mg, 3.6±0.8 mg, 3.6±0.7 mg, 3.6±0.6 mg, 3.6±0.5 mg, 3.6±0.4 mg, 3.6±0.3 mg, 3.6±0.2 mg, or 3.6±0.1 mg (*e.g.*, about 3.6 mg).

[00190] In some aspects, the subject has body weight of 50 kg to 60 kg, and the apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a weekly dose of about 2.6 mg, about 2.7 mg, about 2.8 mg, about 2.9 mg,

about 3.0 mg, about 3.1 mg, about 3.2 mg, about 3.3 mg, about 3.4 mg, about 3.5 mg, about 3.6 mg, about 3.7 mg, about 3.8 mg, about 3.9 mg, about 4.0 mg, about 4.1 mg, about 4.2 mg, about 4.3 mg, about 4.4 mg, about 4.5 mg, or about 4.6 mg.

[00191] In some aspects, subjects with a body weight of 50 kg to 60 kg can be administered apraglutide in an amount from about 2.5 mg to about 5 mg. In some aspects, subjects with a body weight of 50 kg to 60 kg can be administered apraglutide in an amount of about 2.5 mg. In some aspects, subjects with a body weight of 50 kg to 60 kg can be administered apraglutide in an amount of about 5 mg. In some embodiments, the subject has a body weight of 50 kg to 60 kg, and apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a dose of about 3.6 mg.

[00192] In some aspects, subjects with a body weight of 50 kg to 60 kg can be administered apraglutide in an amount from about 2.5 mg to about 5 mg per week. In some aspects, subjects with a body weight of 50 kg to 60 kg can be administered apraglutide in an amount of about 2.5 mg per week. In some aspects, subjects with a body weight of 50 kg to 60 kg can be administered apraglutide in an amount of about 5 mg per week.

[00193] In some aspects, the subject has body weight of 60 kg to 80 kg, and the apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a weekly dose of about 2.5 mg, about 2.6 mg, about 2.7 mg, about 2.8 mg, about 2.9 mg, about 3.0 mg, about 3.1 mg, about 3.2 mg, about 3.3 mg, about 3.4 mg, about 3.5 mg, about 3.6 mg, about 3.7 mg, about 3.8 mg, about 3.9 mg, about 4.0 mg, about 4.1 mg, about 4.2 mg, about 4.3 mg, about 4.4 mg, about 4.5 mg, about 4.6 mg, about 4.7 mg, about 4.8 mg, about 4.9 mg, about 5.0 mg, about 5.1 mg, about 5.2 mg, about 5.3 mg, about 5.4 mg, about 5.5 mg, about 5.6 mg, about 5.7 mg, about 5.8 mg, about 5.9 mg, or about 6.0 mg.

[00194] In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount from about 3.75 mg to about 7.5 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount from about 4 mg to about 7.5 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount from about 2.7 mg to about 5.5 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 2.7 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 3.75 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 4 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide

in an amount of about 5.5 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 7.5 mg.

[00195] In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount from about 3.75 mg to about 7.5 mg per week. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount from about 4 mg to about 7.5 mg per week. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount from about 2.7 mg to about 5.5 mg per week. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 2.7 mg per week. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 3.75 mg. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 4 mg per week. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 5.5 mg per week. In some aspects, subjects with a body weight of 60 kg to 80 kg can be administered apraglutide in an amount of about 7.5 mg per week.

[00196] In some aspects, the subject has body weight of 80 kg or greater, and the apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered at a weekly dose of about 3.5 mg, about 3.6 mg, about 3.7 mg, about 3.8 mg, about 3.9 mg, about 4.0 mg, about 4.1 mg, about 4.2 mg, about 4.3 mg, about 4.4 mg, about 4.5 mg, about 4.6 mg, about 4.7 mg, about 4.8 mg, about 4.9 mg, about 5.0 mg, about 5.1 mg, about 5.2 mg, about 5.3 mg, about 5.4 mg, about 5.5 mg, about 5.6 mg, about 5.7 mg, about 5.8 mg, about 5.9 mg, about 6.0 mg, about 6.1 mg, about 6.2 mg, about 6.3 mg, about 6.4 mg, about 6.5 mg, about 6.6 mg, about 6.7 mg, about 6.8 mg, about 6.9 mg, about 7.0 mg, about 7.1 mg, about 7.2 mg, about 7.3 mg, about 7.4 mg, about 7.5 mg, about 7.6 mg, about 7.7 mg, about 7.8 mg, about 7.9 mg, or about 8.0 mg.

[00197] In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount from about 5 mg to about 10 mg. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount from about 3.6 mg to about 7.6 mg. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount of about 5 mg. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount of about 7.6 mg. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount of about 10 mg.

[00198] In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount from about 5 mg to about 10 mg per week. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount from about 3.6 mg to about 7.6 mg per week. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount of about 5 mg per week. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount of about 7.6 mg per week. In some aspects, subjects with a body weight of 80 kg or greater can be administered apraglutide in an amount of about 10 mg per week.

[00199] In some aspects, subjects may be administered a single dose range from about 1 mg to about 60 mg. In some aspects, subjects may be administered a single dose range from about 1 mg to about 56.9 mg.

[00200] In some aspects, dosing of apraglutide to a subject varies over time. For example, and without limitation, a dose escalation may be appropriate. In another non-limiting example, a dose reduction may be appropriate.

[00201] In some aspects, apraglutide can be administered to a subject in an amount of at least about 0.5, or at least about 1 mg. or at least about 1.5 mg, or at least about 2 mg, or at least about 2.5 mg, or at least about 3 mg, or at least about 3.5 mg, or at least about 4 mg, or at least about 4.5 mg, or at least about 5 mg, or at least about 5.5 mg, or at least about 6 mg, or at least about 6.5 mg, or at least about 7 mg, or at least about 7.5 mg, or at least about 8 mg, or at least about 8.5 mg, or at least about 9 mg, or at least about 9.5 mg, or at least about 10 mg, or at least about 10.5 mg, or at least about 11 mg, or at least about 11.5 mg, or at least about 12 mg, or at least about 12.5 mg, or at least about 13 mg, or at least about 13.5 mg, or at least about 14 mg, or at least about 14.5 mg, or at least about 15 mg, or at least about 15.5 mg, or at least about 16 mg, or least about 16.5 mg, or at least about 17 mg, or at least about 17.5 mg, or at least about 18 mg, or at least about 18.5 mg, or at least about 19 mg, or at least about 19.5 mg, or at least about 20 mg.

[00202] In some aspects, apraglutide can be administered to a subject in an amount of about 0.5, or about 1 mg. or about 1.5 mg, or about 2 mg, or about 2.5 mg, or about 3 mg, or about 3.5 mg, or about 4 mg, or about 4.5 mg, or about 5 mg, or about 5.5 mg, or about 6 mg, or about 6.5 mg, or about 7 mg, or about 7.5 mg, or about 8 mg, or about 8.5 mg, or about 9 mg, or about 9.5 mg, or about 10 mg, or about 10.5 mg, or about 11 mg, or about 11.5 mg, or about 12 mg, or about 12.5 mg, or about 13 mg, or about 13.5 mg, or about 14 mg, or about 14.5 mg, or about 15 mg, or about 15.5 mg, or about 16 mg, or least about 16.5 mg, or about

17 mg, or about 17.5 mg, or about 18 mg, or about 18.5 mg, or about 19 mg, or about 19.5 mg, or about 20 mg.

[00203] In some aspects, apraglutide can be administered to a subject once daily, twice daily, once every two days, once every three days, once every four days, once every five days, once every six days, once every 7 days (once a week), once every 8 days, once every 9 days, once every 10 days, once every 11 days, once every 12 days, once every 13 days, once every 14 days (once every two weeks), once every 15 days, once every 16 days, once every 17 days, once every 18 days, once every 19 days, once every 20 days, once every 21 days (once every three weeks), once every 22 days, once every 23 days, once every 24 days, once every 25 days, once every 26 days, once every 27 days, once every 28 days (once every four weeks), or once a month. In some aspects, apraglutide is administered to a subject once weekly.

Formulation

[00204] In some aspects of the methods and uses of the present disclosure, apraglutide can be administered as part of a pharmaceutical composition. Pharmaceutical compositions of apraglutide can comprise any pharmaceutically acceptable carrier and/or excipient.

[00205] In some aspects of the methods and uses of the present disclosure, the pharmaceutically acceptable salt of apraglutide can be the sodium salt of apraglutide.

[00206] In some aspects of the present disclosure, the pharmaceutically acceptable salt of apraglutide can be a base addition salt, such as the sodium salt of apraglutide.

[00207] A pharmaceutical composition comprising apraglutide or a pharmaceutically acceptable salt thereof, may further comprise at least one pharmaceutically acceptable carrier. In some aspects, the at least one pharmaceutically acceptable carrier is chosen from pharmaceutically acceptable vehicles and pharmaceutically acceptable adjuvants. In some aspects, the at least one pharmaceutically acceptable carrier is chosen from pharmaceutically acceptable fillers, disintegrants, surfactants, binders, lubricants. The term "at least one pharmaceutically acceptable carrier," as used herein, includes any and all solvents, diluents, other liquid vehicles, dispersion aids, suspension aids, surface active agents, isotonic agents, thickening agents, emulsifying agents, preservatives, solid binders, and lubricants, as suited to the particular dosage form desired. Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier is

incompatible with apraglutide, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this disclosure. Non-limiting examples of suitable pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as phosphates, glycine, sorbic acid, and potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts, and electrolytes (such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars (such as lactose, glucose and sucrose), starches (such as corn starch and potato starch), cellulose and its derivatives (such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate), powdered tragacanth, malt, gelatin, talc, excipients (such as cocoa butter and suppository waxes), oils (such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil), glycols (such as propylene glycol and polyethylene glycol), esters (such as ethyl oleate and ethyl laurate), agar, buffering agents (such as magnesium hydroxide and aluminum hydroxide), alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, phosphate buffer solutions, non-toxic compatible lubricants (such as sodium lauryl sulfate and magnesium stearate), coloring agents, releasing agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservatives, and antioxidants. Non-limiting examples of pharmaceutically acceptable carriers and/or excipients include mannitol, glycine, L-histidine or any combination thereof.

[00208] In some aspects, the at least one pharmaceutically acceptable carrier is chosen from glycine, L-Histidine, mannitol, and sodium hydroxide.

[00209] In some aspects of the methods and uses described herein, apraglutide, or a pharmaceutically acceptable salt thereof, is administered as part of a pharmaceutical composition, wherein the pharmaceutical comprises apraglutide, or a pharmaceutically acceptable salt thereof, mannitol, glycine and L-histidine.

[00210] In some aspects, the present disclosure provides a pharmaceutical composition comprising apraglutide of the present disclosure, glycine, L-histidine and mannitol dissolved in water, wherein the concentration of the apraglutide is 25 mg/mL, the concentration of glycine is 3.75 mg/mL, the concentration of L-histidine is 7.75 mg/mL of water and the concentration of mannitol is 115.0 mg/mL. In some embodiments, the volume of water can be

0.5 mL. In some embodiments, the preceding pharmaceutical composition can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[00211] In some aspects, the present disclosure provides a pharmaceutical composition comprising apraglutide of the present disclosure, glycine, L-histidine and mannitol dissolved in water, wherein glycine, L-histidine and mannitol are in a w/w ratio to the weight of apraglutide in the free acid form as follows: glycine, present at a w/w ratio of about 0.15:1; L-histidine, present at a w/w ratio of about 0.31:1, and mannitol, present at a w/w ratio of about 4.6:1. In some embodiments, the preceding pharmaceutical composition can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[00212] In some embodiments, the pharmaceutical composition comprises about 16.5% w/w of apraglutide free acid form; about 2.5% w/w of glycine; about 5.1% w/w of L-histidine; and about 75.9% w/w of mannitol. In some embodiments, the preceding pharmaceutical composition can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[00213] In some embodiments, the pharmaceutical composition comprises the sodium salt of apraglutide, wherein the weight of apraglutide free acid is about 5.2 mg, about 0.78 mg of glycine, about 1.61 mg of L-histidine, and about 23.92 mg of mannitol. In some embodiments, the pharmaceutical composition comprises the sodium salt of apraglutide, wherein the weight of apraglutide free acid is about 10.4 mg, about 1.56 mg of glycine, about 3.22 mg of L-histidine, and about 47.84 mg of mannitol. In some embodiments, the preceding pharmaceutical composition can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[00214] In some embodiments, the pharmaceutical composition comprises about 21 mg/ml of apraglutide free acid, about 3.1 mg/ml of glycine, about 6.4 mg/ml of L-histidine, about 95 mg/ml of mannitol, and sterile water. In some embodiments, the preceding pharmaceutical composition can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[00215] In some embodiments, the pharmaceutical composition comprises about 21 mg/ml of apraglutide free acid, about 3.2 mg/ml of glycine, about 6.5 mg/ml of L-histidine, about 97 mg/ml of mannitol, and sterile water. In some embodiments, the preceding pharmaceutical composition can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[00216] In some embodiments, the osmolarity of a pharmaceutical composition of the present disclosure is between 290 - 780 mOsmol/kg. In some embodiments, the osmolarity of

a pharmaceutical composition of the present disclosure is about 780 mOsmol/kg. In some embodiments, the osmolarity of a pharmaceutical composition of the present disclosure is about 780 ± 160 mOsmol/kg.

[00217] The GLP-2 analog peptide composition for injection may be an aseptically manufactured lyophilized powder for solution for injection. It can be presented in a colorless glass vial suitable for a lyophilized sterile product, closed with a rubber stopper and sealed with an aluminum cap. Prior to administration, the GLP-2 analog peptide for injection may be dissolved in about 0.5 mL of sterile Water for Injection (sWFI). The reconstituted solution may be administered subcutaneously.

[00218] The compounds or the corresponding pharmaceutical compositions taught herein can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

[00219] The pharmaceutical composition of the application is formulated to be compatible with its intended route of administration. The composition may be formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. In preferred aspects, the pharmaceutical composition is formulated for intravenous administration.

[00220] The oral therapeutic administration may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[00221] The parenteral administration may be generally prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00222] The injectable administration may be prepared as a sterile aqueous solution or dispersion thereof, and sterile powders of, apraglutide for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

[00223] Apraglutide can be administered via subcutaneous injection. For example, apraglutide can be administered *via* single-dose bolus subcutaneous injection.

[00224] Suitable sites for subcutaneous injection include the four quadrants of the abdomen and thighs. In some embodiments, apraglutide, or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is administered subcutaneously, alternating between the four quadrants of the abdomen. In some embodiments, apraglutide, the pharmaceutically acceptable thereof, or a pharmaceutical composition comprising the same, is administered subcutaneously, alternating between thighs.

[00225] Apraglutide can be administered via a two-chamber syringe or dual cartridge injector. One example of such a syringe is described in PCT/EP2012/000787, the contents of which are incorporated herein by reference.

[00226] GLP-2 agonists, *e.g.*, apraglutide, may be administered parenterally, *e.g.*, by injection. Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostatics, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Liquid carriers, for injectable solutions, include by way of example and without limitation water, saline, aqueous dextrose and glycols.

[00227] Apraglutide can be administered as part of a pharmaceutical composition. Pharmaceutical compositions of apraglutide can comprise any pharmaceutically acceptable carrier and/or excipient. Pharmaceutical compositions of apraglutide can comprise glycine, L-histidine, mannitol, and any combination thereof.

[00228] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Included in this definition are benign and malignant cancers. Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, leukemia and germ cell tumors. More particular examples of such cancers include adrenocortical carcinoma, bladder urothelial carcinoma, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, esophageal carcinoma, glioblastoma multiforme, head and neck squamous cell

carcinoma, kidney chromophobe, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, acute myeloid leukemia, brain lower grade glioma, liver hepatocellular carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma, paraganglioma, prostate adenocarcinoma, rectum adenocarcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine carcinosarcoma, uveal melanoma. Other examples include breast cancer, lung cancer, lymphoma, melanoma, liver cancer, colorectal cancer, ovarian cancer, bladder cancer, renal cancer or gastric cancer. Further examples of cancer include neuroendocrine cancer, non-small cell lung cancer (NSCLC), small cell lung cancer, thyroid cancer, endometrial cancer, biliary cancer, esophageal cancer, anal cancer, salivary, cancer, vulvar cancer, cervical cancer, Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML), Adrenal gland tumors, Anal cancer, Bile duct cancer, Bladder cancer, Bone cancer, Bowel cancer, Brain tumors, Breast cancer, Cancer of unknown primary (CUP), Cancer spread to bone, Cancer spread to brain, Cancer spread to liver, Cancer spread to lung, Carcinoid, Cervical cancer, Children's cancers, Chronic lymphocytic leukemia (CLL), Chrome myeloid leukemia (CML), Colorectal cancer, Ear cancer, Endometrial cancer, Eye cancer, Follicular dendritic cell sarcoma, Gallbladder cancer, Gastric cancer, Gastro esophageal junction cancers, Germ cell tumors, Gestational trophoblastic disease (GIT)), Hairy cell leukemia, Head and neck cancer, Hodgkin lymphoma, Kaposi's sarcoma, Kidney cancer, Laryngeal cancer, Leukemia, Gastric linitis plastica, Liver cancer, Lung cancer, Lymphoma, Malignant schwannoma, Mediastinal germ cell tumors, Melanoma skin cancer, Men's cancer, Merkel cell skin cancer, Mesothelioma, Molar pregnancy, Mouth and oropharyngeal cancer, Myeloma, Nasal and paranasal sinus cancer, Nasopharyngeal cancer, Neuroblastoma, Neuroendocrine tumors, Non-Hodgkin lymphoma (NHL), Esophageal cancer, Ovarian cancer, Pancreatic cancer, Penile cancer, Persistent trophoblastic disease and choriocarcinoma, Pheochromocytoma, Prostate cancer, Pseudomyxoma peritonei, Rectal cancer. Retinoblastoma, Salivary gland cancer, Secondary' cancer, Signet cell cancer, Skin cancer, Small bowel cancer, Soft tissue sarcoma, Stomach cancer, T cell childhood non Hodgkin lymphoma (NHL), Testicular cancer, Thymus gland cancer, Thyroid cancer, Tongue cancer, Tonsil cancer, Tumors of the adrenal gland, Uterine cancer. Vaginal cancer, Vulval cancer, Wilms' tumor, Womb cancer and Gynaecological cancer. Examples of cancer also include, but are not limited to, Hematologic malignancies, Lymphoma, Cutaneous T-cell lymphoma, Peripheral T-cell lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Multiple myeloma, Chrome lymphocytic leukemia, chronic

myeloid leukemia, acute myeloid leukemia, Myelodysplastic syndromes, Myelofibrosis, Biliary tract cancer, Hepatocellular cancer, Colorectal cancer, Breast cancer, Lung cancer, Non-small cell lung cancer, Ovarian cancer, Thyroid Carcinoma, Renal Cell Carcinoma, Pancreatic cancer, Bladder cancer, skin cancer, malignant melanoma, merkel cell carcinoma, Uveal Melanoma or Glioblastoma multiforme.

[00229] In some aspects, the cancer is a carcinoma, a lymphoma, a blastoma, a sarcoma, a leukemia, a brain cancer, a breast cancer, a blood cancer, a bone cancer, a lung cancer, a skin cancer, a liver cancer, an ovarian cancer, a bladder cancer, a renal cancer, a kidney cancer, a gastric cancer, a thyroid cancer, a pancreatic cancer, an esophageal cancer, a prostate cancer, a cervical cancer, a uterine cancer, a stomach cancer, a soft tissue cancer, a laryngeal cancer, a small intestine cancer, a testicular cancer, an anal cancer, a vulvar cancer, a joint cancer, an oral cancer, a pharynx cancer or a colorectal cancer.

[00230] In some aspects, the cancer is a hematological cancer.

[00231] In some aspects, the cancer is Acute myeloid leukemia, myelodysplastic syndrome, follicular lymphoma, diffuse large B cell lymphoma, acute lymphoblastic leukemia, multiple myeloma, Hodgkin lymphoma, chronic myeloid leukemia, T cell non-Hodgkin lymphoma, lymphoblastic B cell non-Hodgkin lymphoma (non-Burkitt), Burkitt's lymphoma, anaplastic large cell lymphoma, germ cell tumor, Ewing's sarcoma, soft tissue sarcoma, neuroblastoma, Wilms' tumor, osteosarcoma, medulloblastoma, acute promyelocytic leukemia, mantle cell lymphoma, T cell lymphoma, lymphoplasmacytic lymphoma, cutaneous T cell lymphoma, plasmablastic lymphoma, chronic lymphocytic leukemia, breast cancer and renal cancer.

[00232] In some aspects, a disease or disorder is a hemoglobinopathy, a congenital hemoglobinopathy, β-Thalessemia major (TM), sickle cell disease (SCD), severe aplastic anemia, Fanconi's anemia, dyskeratosis congenita, Blackfan-Diamond anemia, Thalassemia, congenital amegakaryocytic thrombocytopenia, severe combined immunodeficiency, T cell immunodeficiency, T cell immunodeficiency-SCID variants, Wiskott-Aldrich syndrome, a hemophagocytic disorder, a lymphoproliferative disorder, severe congenital neutropenia, chronic granulomatous disease, a phagocytic cell disorder, IPEX syndrome, juvenile rheumatoid arthritis, systemic sclerosis, an autoimmune disorder, an immune dysregulation disorder, mucopolysaccharoidoses, MPS-I, MPS-VI, osteopetrosis, a metabolic disease, globoid cell leukodystrophy (Krabbe), metachromatic leukodystrophy, cerebral X-linked adrenoleukodystrophy, a myelofibrosis disease, a myeloproliferative disease, a plasma cell disorder, a mast cell disease, common variable immunodeficiency, chronic granulomatous

disease, multiple sclerosis, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease or polymyositis-dermatomyositis.

[00233] As used herein, the term "temporal proximity" refers to that administration of one therapeutic composition (*e.g.*, apraglutide, or a pharmaceutically acceptable salt thereof) occurs within a time period before or after the administration of another therapeutic composition (*e.g.*, a transplant, a conditioning therapy, a second active agent), such that the therapeutic effect of the one therapeutic agent overlaps with the therapeutic effect of the other therapeutic agent. In some embodiments, the therapeutic effect of the one therapeutic agent completely overlaps with the therapeutic effect of the other therapeutic agent. In some embodiments, "temporal proximity" means that administration of one therapeutic agent occurs within a time period before or after the administration of another therapeutic agent, such that there is a synergistic effect between the one therapeutic agent and the other therapeutic agent. "Temporal proximity" may vary according to various factors, including but not limited to, the age, gender, weight, genetic background, medical condition, disease history, and treatment history of the subject to which the therapeutic agents are to be administered; the disease or condition to be treated or ameliorated; the therapeutic outcome to be achieved; the dosage, dosing frequency, and dosing duration of the therapeutic agents; the pharmacokinetics and pharmacodynamics of the therapeutic agents; and the route(s) through which the therapeutic agents are administered. In some embodiments, "temporal proximity" means within 15 minutes, within 30 minutes, within an hour, within two hours, within four hours, within six hours, within eight hours, within 12 hours, within 18 hours, within 24 hours, within 36 hours, within 2 days, within 3 days, within 4 days, within 5 days, within 6 days, within a week, within 2 weeks, within 3 weeks, within 4 weeks, with 6 weeks, or within 8 weeks.

[00234] In some embodiments, multiple administrations of one therapeutic agent can occur in temporal proximity to a single administration of another therapeutic agent. In some embodiments, temporal proximity may change during a treatment cycle or within a dosing regimen.

EXAMPLES

[00235] The following Examples are merely illustrative and are not intended to limit the scope or content of the disclosure in any way.

Example 1 – Assessment of Safety and Efficacy of Apraglutide in GvHD

[00236] Safety and efficacy of apraglutide was evaluated in subjects with Grade II to IV Mount Sinai aGVHD International Consortium (MAGIC) score, specifically, with lower

gastrointestinal (lower GI) aGVHD. Subjects were receiving standard of care systemic steroids (SS) and ruxolitinib (RUX). Subjects were steroid-refractory.

[00237] Inclusion Criteria for the randomized, double-blind Phase 2 study of apraglutide included:

1. Participants were aged 12 years or above at the time of consent and weighed a minimum of 40 kg;

2. Participants had undergone or were undergoing alloSCT from any donor source (including but not limited to matched unrelated donor, sibling, haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood. Recipients of non-myeloablative, myeloablative, and reduced intensity conditioning were eligible;

3. Participants had evident myeloid and platelet engraftment (confirmed prior to trial medication start) as determined by:

a) Absolute neutrophil count >1,000/mm^3; and

b) Platelets ≥20,000/mm^3;

4. Participants were permitted use of growth factor supplementation (granulocyte-colony stimulating factor and granulocyte-macrophage-colony stimulating factor) and transfusion support;

5. Participants had histologically diagnosed GI-aGVHD at screening (with clinically confirmed SR GI-aGVHD at ruxolitinib start and prior to apraglutide start) which was defined as subjects administered SS, given alone or combined with calcineurin inhibitors (CNI) and either:

a) Disease progression based on organ assessment after 3 days of systemic methylprednisolone (MP) of 2mg/kg +/- CNI; or

b) No improvement after 7 days of treatment with MP 2mg/kg/day equivalent; or

c) Progressed to a new organ after treatment with MP 2 mg/kg/day equivalent for skin and upper GI-aGVHD; or

d) Recurred during or after a steroid taper.

All subjects were Stage 1–4 lower GI-aGVHD at enrollment.

6. Participants were treated with systemic steroids (SS) plus ruxolitinib (RUX) (RUX was administered at the recommended dose 2 twice daily for 0–3 days prior to beginning apraglutide treatment).

Calcineurin inhibitors were allowed as co-medication, if needed.

[00238] Participants weighing ≥50.0 kg were randomized to one of two treatment arms (low dose or high dose, within three body weight bands). The exact dose received at each visit depended upon the weight band the individual subject fell into (*see* **Table 3**). Participants weighing 40.0–49.9 kg received apraglutide at 1.5 mg or 2.5 mg.

[00239] Apraglutide was administered at a dose of 1.5 mg, 2.5 mg, 2.7 mg, 3.6 mg, 4.0 mg, 5.0 mg, 5.5 mg, 7.5 mg, 7.6 mg, or 10.0 mg, subcutaneously, once weekly. Administration of apraglutide was for 8-13 weeks.

Table 3. Dose of Investigational Medicinal Product Based on Treatment Arm and Weight

Treatment Arm	**Weight Band (based on Baseline Weight)**			
	40.0-<50.0 kg	**50.0-<60.0 kg**	**60.0 – 80.0 kg**	**>80.0 kg**
Low dose (mg)	1.5 or 2.5	1.5 or 2.5	2.7 or 4	3.6 or 5
High dose (mg)		3.6 or 5	5.5 or 7.5	7.6 or 10

[00240] Subjects underwent screening assessments during a 14-day Screening Period, with screening assessments including, but not limited to, analysis of analysis of vital signs, height and weight, colonoscopy, gut biopsy, medical history, *etc*.

[00241] Apraglutide was given as an add-on-therapy to RUX and SS. Systemic steroid dose adjustments were permitted at the Investigator's discretion, and topical steroids were added as needed. Ruxolitinib was administered in accordance with national guidelines (including dose adjustments). Apraglutide was administered concomitantly to RUX, or, if concomitant administration was not possible, RUX was administered at maximum 72 hours prior to apraglutide initiation. Comparison to RUX and SS only was through historical control (*see,* for example, Zeiser *et al*., (2020) *NEJM*, 382:1800-1810). A schematic depiction of the trial design is shown in **FIG. 1**.

[00242] 31 subjects participated in the study. 27 / 31 (87.1%) had MAGIC Grade III or IV aGVHD, and 20 / 31 (64.5%) had Lower GI Stage 3 or 4 GvHD.

[00243] Subjects were divided by body weight, and low body weight subjects (below 50 kg) were dosed with 1.5 or 2.5 mg apraglutide. Subjects with body weight greater than 50 kg were randomly assigned to the low dose or high dose of apraglutide (doses provided in **Table 3** above). Mean number of days from Lower GI-aGVHD Diagnosis to when subjects became Steroid Refractory was 16.1 ± 13.8 for the low dose arm, and 6.9 ± 6.1 for the high dose arm. Mean dose (mg/day) for systemic steroids at randomization was 91.9 ± 51.7 for the low dose

arm, and 129.6 ± 52.6 for the high dose arm. The higher steroid dose and shorter time to steroid refractory might be indicative of a more aggressive disease at baseline in the high dose group.

[00244] Treatment with apraglutide, RUX, and SS was through an initial end at day 56 (week 8), and subjects with complete response (CR) in the GI stopped apraglutide. Treatment was extended at investigator's discretion for subject's without CR to week 12; subjects with CR at week 12 stopped apraglutide. Treatment with apraglutide was extended at the investigator's discretion until CR or to a maximum of 25-weeks. Two patients continued the 25-week term.

[00245] Apraglutide was well-tolerated. The majority of adverse events were non-serious, and the safety profile was consistent with that of the underlying GvHD, background RUX treatment, and known safety profile of GLP-2 agonists. Most adverse events were assessed as not related to apraglutide; only 16 nonserious and 1 SAE were assessed as related. Events leading to discontinuation occurred equally in the high and low dose groups, and most were considered not related to apraglutide. 11 subjects had fatal events, and all were assessed as not related to apraglutide.

[00246] Using the MAGIC classification system (*i.e.*, organ stages 0 to 4, as detailed in Table 1 *supra*) a complete responder (CR) on lower GI was stage 0, and a partial responder (PR) on lower GI had an improvement of 1 stage as compared to baseline (day 0). For all organs, CR was stage 0 in all organs, and PR was an improvement of 1 stage in any organ without a worsening in another organ compared to baseline. A non-responder had stable disease or disease progression, additional therapies were added, or stopped the study due to withdrawal or death.

[00247] A remarkably durable effect of apraglutide was observed for both dose levels tested. For the lower GI MAGIC Score, there was a strong overall responder (both CR and PR) rate at day 28 of treatment. The improved GI response is maintained to day 56, and at least to day 91 (**FIG. 2A**, **FIG. 2B**).

[00248] All-organ response, as shown in **FIG. 3**, was largely driven by the lower GI response, as efficacy was substantially equal between the lower GI response or the all-organ Response (**FIG. 2B, FIG. 3**). As shown, all-organ response demonstrated high levels of overall responders until about day 90. Without wishing to be bound by theory, the beginning of a decline in response may be attributable to deterioration in organs other than the GI tract where apraglutide functions.

[00249] Individual subject response durability is depicted in **FIG. 4A – FIG. 4B** (lower GI response) and **FIG. 4C – FIG. 4D** (all-organ response).

[00250] Details of lower GI response observed for the three arms of the study at days 28, 56, and 91 are provided in **Table 4**, **Table 5**, and **Table 6**, respectively. Details of all-organ response for the three arms of the study at days 28, 56, and 91 are provided in **Table 7**, **Table 8**, and **Table 9,** respectively.

Table 4. Lower GI response, Day 28

Response Stage		**Randomized**				
		Low Dose (N=15)	**High Dose (N=15)**	**Total (N=30)**	**Low Body Weight (N=1)**	**Total (N=31)**
Overall Responder	**n (%)**	**10 (66.7)**	**6 (40.0)**	**16 (53.3)**	**1 (100)**	**17 (54.8)**
Complete Response	95% CI	(38.4, 88.2)	(16.3, 67.7)	(34.3, 71.7)	(2.5, 100)	(36.0, 72.7)
	n (%)	6 (40.0)	2 (13.3)	8 (26.7)	1 (100)	9 (29.0)
	95% CI	(16.3, 67.7)	(1.7, 40.5)	(12.3, 45.9)	(2.5, 100)	(14.2, 48.0)
Partial Response	n (%)	4 (26.7)	4 (26.7)	8 (26.7)	0 (0)	8 (25.8)
	95% CI	(7.8, 55.1)	(7.8, 55.1)	(12.3, 45.9)	(0, 97.5)	(11.9, 44.6)
Overall Non-Responder	**n (%)**	**5 (33.3)**	**9 (60.0)**	**14 (46.7)**	**0 (0)**	**14 (45.2)**
Stable Disease	n (%)	1 (6.7)	5 (33.3)	6 (20.0)	0 (0)	6 (19.4)
Progression	n (%)	0 (0)	1 (6.7)	1 (3.3)	0 (0)	1 (3.2)
Death	n (%)	1 (6.7)	2 (13.3)	3 (10.0)	0 (0)	3 (9.7)
Treatment Failure	n (%)	1 (6.7)	0 (0)	1 (3.3)	0 (0)	1 (3.2)
Missing	n (%)	2 (13.3)	1 (6.7)	3 (10.0)	0 (0)	3 (9.7)

Table 5. Lower GI response, Day 56

Response Stage		**Randomized**				
		Low Dose (N=15)	**High Dose (N=15)**	**Total (N=30)**	**Low Body Weight (N=1)**	**Total (N=31)**
Overall Responder	**n (%)**	**8 (53.3)**	**7 (46.7)**	**15 (50.0)**	**1 (100)**	**16 (51.6)**
	95% CI	(26.6, 78.7)	(21.3, 73.4)	(31.3, 68.7)	(2.5, 100)	(33.1, 69.8)
Complete Response	n (%)	5 (33.3)	3 (20.0)	8 (26.7)	1 (100)	9 (29.0)
	95% CI	(11.8, 61.6)	(4.3, 48.1)	(12.3, 45.9)	(2.5, 100)	(14.2, 48.0)
Partial Response	n (%)	3 (20.0)	4 (26.7)	7 (23.3)	0 (0)	7 (22.6)
	95% CI	(4.3, 48.1)	(7.8, 55.1)	(9.9, 42.3)	(0, 97.5)	(9.6, 41.1)
Overall Non-Responder	**n (%)**	**7 (46.7)**	**8 (53.3)**	**15 (50.0)**	**0 (0)**	**15 (48.4)**
Stable Disease	n (%)	1 (6.7)	1 (6.7)	2 (6.7)	0 (0)	2 (6.5)
Progression	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death	n (%)	1 (6.7)	4 (26.7)	5 (16.7)	0 (0)	5 (16.1)

Treatment Failure	n (%)	1 (6.7)	1 (6.7)	2 (6.7)	0 (0)	2 (6.5)
Missing	n (%)	4 (26.7)	2 (13.3)	6 (20.0)	0 (0)	6 (19.4)

Table 6. Lower GI response, Day 91

Response Stage		**Randomized**				
		Low Dose (N=15)	**High Dose (N=15)**	**Total (N=30)**	**Low Body Weight (N=1)**	**Total (N=31)**
Overall Responder	**n (%)**	**7 (46.7)**	**7 (46.7)**	**14 (46.7)**	**1 (100)**	**15 (48.4)**
	95% CI	(21.3, 73.4)	(21.3, 73.4)	(28.3, 65.7)	(2.5, 100)	(30.2, 66.9)
Complete Response	n (%)	7 (46.7)	2 (13.3)	9 (30.0)	1 (100)	10 (32.3)
	95% CI	(21.3, 73.4)	(1.7, 40.5)	(14.7, 49.4)	(2.5, 100)	(16.7, 51.4)
Partial Response	n (%)	0 (0)	5 (33.3)	5 (16.7)	0 (0)	5 (16.1)
	95% CI	(0, 21.8)	(11.8, 61.6)	(5.6, 34.7)	(0, 97.5)	(5.5, 33.7)
Overall Non-Responder	**n (%)**	**8 (53.3)**	**8 (53.3)**	**16 (53.3)**	**0 (0)**	**16 (51.6)**
Stable Disease	n (%)	0 (0)	1 (6.7)	1 (3.3)	0 (0)	1 (3.2)
Progression	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death	n (%)	1 (6.7)	4 (26.7)	5 (16.7)	0 (0)	5 (16.1)
Treatment Failure	n (%)	1 (6.7)	1 (6.7)	2 (6.7)	0 (0)	2 (6.5)
Missing	n (%)	6 (40.0)	2 (13.3)	8 (26.7)	0 (0)	8 (25.8)

Table 7. All-organ response, Day 28

Response Stage		**Randomized**				
		Low Dose (N=15)	**High Dose (N=15)**	**Total (N=30)**	**Low Body Weight (N=1)**	**Total (N=31)**
Overall Responder	**n (%)**	**10 (66.7)**	**7 (46.7)**	**17 (56.7)**	**1 (100)**	**18 (58.1)**
	95% CI	(38.4, 88.2)	(21.3, 73.4)	(37.4, 74.5)	(2.5, 100)	(39.1, 75.5)
Complete Response	n (%)	5 (33.3)	2 (13.3)	7 (23.3)	1 (100)	8 (25.8)
	95% CI	(11.8, 61.6)	(1.7, 40.5)	(9.9, 42.3)	(2.5, 100)	(11.9, 44.6)
Partial Response	n (%)	5 (33.3)	5 (33.3)	10 (33.3)	0 (0)	10 (32.3)
	95% CI	(11.8, 61.6)	(11.8, 61.6)	(17.3, 52.8)	(0, 97.5)	(16.7, 51.4)
Overall Non-Responder	**n (%)**	**5 (33.3)**	**8 (53.3)**	**13 (43.3)**	**0 (0)**	**13 (41.9)**
Stable Disease	n (%)	1 (6.7)	4 (26.7)	5 (16.7)	0 (0)	5 (16.1)
Mixed Response	n (%)	0 (0)	1 (6.7)	1 (3.3)	0 (0)	1 (3.2)
Progression	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death	n (%)	1 (6.7)	2 (13.3)	3 (10.0)	0 (0)	3 (9.7)
Treatment Failure	n (%)	1 (6.7)	0 (0)	1 (3.3)	0 (0)	1 (3.2)

Missing	n (%)	2 (13.3)	1 (6.7)	3 (10.0)	0 (0)	3 (9.7)

Table 8. All-organ response, Day 56

Response Stage		**Randomized**				
		Low Dose (N=15)	**High Dose (N=15)**	**Total (N=30)**	**Low Body Weight (N=1)**	**Total (N=31)**
Overall Responder	**n (%)**	**8 (53.3)**	**7 (46.7)**	**15 (50.0)**	**1 (100)**	**16 (51.6)**
	95% CI	(26.6, 78.7)	(21.3, 73.4)	(31.3, 68.7)	(2.5, 100)	(33.1, 69.8)
Complete Response	n (%)	5 (33.3)	3 (20.0)	8 (26.7)	1 (100)	9 (29.0)
	95% CI	(11.8, 61.6)	(4.3, 48.1)	(12.3, 45.9)	(2.5, 100)	(14.2, 48.0)
Partial Response	n (%)	3 (20.0)	4 (26.7)	7 (23.3)	0 (0)	7 (22.6)
	95% CI	(4.3, 48.1)	(7.8, 55.1)	(9.9, 42.3)	(0, 97.5)	(9.6, 41.1)
Overall Non-Responder	**n (%)**	**7 (46.7)**	**8 (53.3)**	**15 (50.0)**	**0 (0)**	**15 (48.4)**
Stable Disease	n (%)	1 (6.7)	1 (6.7)	2 (6.7)	0 (0)	2 (6.5)
Mixed Response	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Progression	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death	n (%)	1 (6.7)	4 (26.7)	5 (16.7)	0 (0)	5 (16.1)
Treatment Failure	n (%)	1 (6.7)	1 (6.7)	2 (6.7)	0 (0)	2 (6.5)
Missing	n (%)	4 (26.7)	2 (13.3)	6 (20.0)	0 (0)	6 (19.4)

Table 9. All-organ response, Day 91

Response Stage		**Randomized**				
		Low Dose (N=15)	**High Dose (N=15)**	**Total (N=30)**	**Low Body Weight (N=1)**	**Total (N=31)**
Overall Responder	**n (%)**	**6 (40.0)**	**7 (46.7)**	**13 (43.3)**	**1 (100)**	**14 (45.2)**
	95% CI	(16.3, 67.7)	(21.3, 73.4)	(25.5, 62.6)	(2.5, 100)	(27.3, 64.0)
Complete Response	n (%)	6 (40.0)	2 (13.3)	8 (26.7)	1 (100)	9 (29.0)
	95% CI	(16.3, 67.7)	(1.7, 40.5)	(12.3, 45.9)	(2.5, 100)	(14.2, 48.0)
Partial Response	n (%)	0 (0)	5 (33.3)	5 (16.7)	0 (0)	5 (16.1)
	95% CI	(0, 21.8)	(11.8, 61.6)	(5.6, 34.7)	(0, 97.5)	(5.5, 33.7)
Overall Non-Responder	**n (%)**	**9 (60.0)**	**8 (53.3)**	**17 (56.7)**	**0 (0)**	**17 (54.8)**
Stable Disease	n (%)	0 (0)	1 (6.7)	1 (3.3)	0 (0)	1 (3.2)
Mixed Response	n (%)	1 (6.7)	0 (0)	1 (3.3)	0 (0)	1 (3.2)
Progression	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death	n (%)	1 (6.7)	4 (26.7)	5 (16.7)	0 (0)	5 (16.1)
Treatment Failure	n (%)	1 (6.7)	1 (6.7)	2 (6.7)	0 (0)	2 (6.5)

Missing	n (%)	6 (40.0)	2 (13.3)	8 (26.7)	0 (0)	8 (25.8)

[00251] Taken together, these data demonstrate the first prospective trial of a glucagon-like peptide (GLP-2) analog in steroid-refractory aGVHD. For the tested dose groups, the majority of subjects responded to apraglutide treatment by day 28 and day 56. The response on the lower GI tract is maintained from day 28 to day 56, and through at least day 91.

EQUIVALENTS

[00252] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference. The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

WHAT IS CLAIMED IS:

1. Apraglutide, or a pharmaceutically acceptable salt thereof, for use in the treatment of Graft versus Host Disease (GvHD) in a subject,

wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered once weekly,

wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered concurrently with ruxolitinib, and

wherein the administration of apraglutide or pharmaceutically acceptable salt thereof results in a decreased lower gastrointestinal (lower GI) MAGIC clinical stage compared to baseline for at least 90 days after initiation of treatment.

2. A method of treating Graft versus Host Disease (GvHD) in a subject, the method comprising:

administering the apraglutide, or a pharmaceutically acceptable salt thereof, once weekly to the subject,

wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered concurrently with ruxolitinib, and

wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof results in a decreased lower gastrointestinal (lower GI) MAGIC clinical stage compared to baseline for at least 90 days after initiation of treatment.

3. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of claim 1 or 2, wherein:

(a) the subject has a body weight of less than 50 kg, and the apraglutide is administered at a dose of about 2.5 mg;

(b) the subject has a body weight of about 50 kg to about 60 kg, and the apraglutide is administered at a dose of about 2.5 mg or about 5 mg;

(c) the subject has a body weight of about 60 kg to about 80 kg, and the apraglutide is administered at a dose of about 4 mg or about 7.5 mg; or

(d) the subject has a body weight of greater than 80 kg, and the apraglutide is administered at a dose of about 5 mg or about 10 mg.

4. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of claim 1 or 2, wherein:

(a) the subject has a body weight of less than 50 kg, and the apraglutide is administered at a dose of about 1.5 mg;

(b) the subject has a body weight of about 50 kg to about 60 kg, and the apraglutide is administered at a dose of about 1.5 mg or about 3.6 mg;

(c) the subject has a body weight of about 60 kg to about 80 kg, and the apraglutide is administered at a dose of about 2.7 mg or about 5.5 mg; or

(d) the subject has a body weight of greater than 80 kg, and the apraglutide is administered at a dose of about 3.6 mg or about 7.6 mg.

5. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-4, further comprising administering one or more systemic steroids to the subject.

6. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-5, wherein the GvHD is acute GvHD.

7. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-6, wherein the GvHD is acute gastrointestinal GvHD.

8. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-7, wherein the GvHD is steroid-refractory.

9. The method or apraglutide for use of any one of claims 1-8, wherein the baseline is stage 1-4 GvHD according to the MAGIC scale for lower GI, and after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased to stage 0.

10. The method or apraglutide for use of any one of claims 1-9, wherein the baseline is stage 1-4 GvHD according to the MAGIC scale for lower GI, and after the administration of apraglutide or a pharmaceutically acceptable salt thereof, the GvHD is decreased by at least one stage.

11. The method or apraglutide for use of any one of claims 1-10, wherein the subject has a complete response to treatment.

12. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-11, wherein the subject has a partial response to treatment.

13. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-12, wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof results in a decreased all-organ MAGIC clinical score for at least about 90 days after initiation of treatment.

14. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-13, wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof maintains the decreased MAGIC lower GI stage for at least about 3× as many days as a subject administered ruxolitinib only.

15. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-14, wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof decreases relapse compared to a subject administered ruxolitinib only.

16. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-15, wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof decreases mortality compared to a subject administered ruxolitinib only.

17. The method or apraglutide for use of any one of claims 1-16, wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof increases overall survival compared to a subject administered ruxolitinib only.

18. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-7 or 9-17, wherein the GvHD is steroid-naive.

19. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-5 or 8-18, wherein the GvHD is chronic GvHD.

20. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-19, wherein the apraglutide, or pharmaceutically acceptable salt thereof, is administered to the subject prior to the subject being administered radiation therapy, chemotherapy, or radiomimetic therapy in connection with a transplant.

21. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-20, wherein the subject has been previously administered a transplant, optionally wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered to the subject after the subject has been administered a transplant.

22. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-21, wherein the subject has been previously administered radiation therapy, chemotherapy, radiomimetic therapy or any combination thereof in connection with a transplant, optionally wherein the apraglutide or a pharmaceutically acceptable salt thereof is administered to the subject after the subject has been administered radiation therapy, chemotherapy radiomimetic therapy or any combination thereof.

23. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-22, wherein the administration of apraglutide or a pharmaceutically acceptable salt thereof prevents and/or attenuates a reduction in colon length in a subject following:

(a) a transplant; and/or

(b) a conditioning therapy and a transplant.

24. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-23, wherein the transplant comprises hematopoietic stem cells derived from bone marrow, peripheral blood, umbilical cord blood or any combination thereof, optionally wherein the transplant comprises T-cells, and optionally wherein the T-cells are chimeric antigen receptor (CAR) T-cells.

25. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 20-24, wherein the radiation therapy comprises total body irradiation.

26. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-25, wherein the pharmaceutically acceptable salt of apraglutide is the sodium salt of apraglutide.

27. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-26, wherein the apraglutide or pharmaceutically acceptable salt thereof is administered by subcutaneous injection.

28. The method or apraglutide, or pharmaceutically acceptable salt thereof, for use of any one of claims 1-27, wherein the transplant is:

(a) an allogeneic transplant; or

(b) an autologous transplant.