DOSAGE REGIMENS FOR GLUCAGON-LIKE PEPTIDE 2 (GLP-2) ANALOGS

RELATED APPLICATIONS

[0001] This application claims the priority to, and benefit of, U.S. Provisional Application No. 63/559,743, filed on February 29, 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-005_001WO_SeqListST26.xml; Size: 3,930 bytes; and Date of Creation: February 10, 2025) is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0003] The present disclosure relates to dosage regimens for glucagon-like-peptide-2 (GLP-2) analogs, *e.g.*, apraglutide, in a subject in need thereof, *e.g.*, a subject with short bowel syndrome (SBS).

BACKGROUND

[0004] Glucagon-like peptide 2 (GLP-2) is a 33-amino-acid peptide released from the post-translational processing of proglucagon in the enteroendocrine L cells of the intestine.

[0005] Short bowel syndrome is a malabsorptive condition characterized by extreme reduction in functional intestinal length most commonly as a result of surgical resection due to mesenteric ischemia or Inflammatory Bowel Disease (IBD) although other etiologies are also present. SBS with intestinal failure (SBS-IF) is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or fluids and electrolytes, such that intravenous supplementation is required to maintain health and/or growth.

[0006] In patients with SBS-IF, parenteral support (PS) delivered through a central venous catheter is needed to maintain an adequate fluid, energy, electrolytes, trace elements, vitamins, and nutrient balance. There is a spectrum of SBS-IF patients, from those with stoma and no colon-in-continuity (CIC) requiring large PS volumes to those with CIC requiring lower PS volumes. As a consequence of this spectrum, decreased dependency on PS can be demonstrated in a variety of outcomes depending on anatomy, including PS volume reduction, days off PS, or achieving enteral autonomy. After surgical resection, the remaining intestine goes through a process called intestinal adaptation by which it increases its absorptive capacity to compensate for its reduced length.

[0007] It has been demonstrated that this process of intestinal adaptation can be enhanced by administering glucagon-like peptide 2 (GLP-2) or more stable analogs with extended half-lives, such as teduglutide, glepaglutide, elsiglutide, and apraglutide. The composition of apraglutide, and physiological effects thereof, are described, for example, in WO 2021/252659.

[0008] Further elucidation of specific uses (*e.g.*, dosing) of GLP-2 analogs such as apraglutide and the effects of such uses, such as effects on parenteral support, are required.

SUMMARY OF THE DISCLOSURE

[0009] In some aspects, provided herein is a glucagon-like peptide 2 (GLP-2) analog for use in a method of treating short bowel syndrome (SBS) in a subject receiving parenteral support (PS), comprising: administering the GLP-2 analog to the subject receiving an existing volume and frequency of the PS for a period of time; and modifying the volume and/or frequency of the PS, comprising: measuring a produced daily urine volume of the subject upon administering the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume, thereby determining a daily urine production change; and determining a modified volume and/or frequency of the PS, wherein: when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change; when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then: the modified volume and frequency of the PS equals the existing volume and frequency of the PS; the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS. In some embodiments, calorie content of the PS is increased or decreased.

[0010] In another aspect, provided herein is a method of treating short bowel syndrome (SBS) in a subject receiving a parenteral support (PS), comprising: administering a glucagon-like peptide 2 (GLP-2) analog to the subject receiving an existing volume and frequency of the PS for a period of time; and modifying the volume and/or frequency of the PS, comprising: measuring a produced daily urine volume of the subject upon administering the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume, thereby determining a daily urine production change; and determining a modified volume and/or frequency of the PS, wherein: when the daily urine production change is about 10% increase

or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change; when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then: the modified volume and frequency of the PS equals the existing volume and frequency of the PS; the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS. In some embodiments, calorie content of the PS is increased or decreased.

[0011] In another aspect, provided herein is a combination of a glucagon-like peptide 2 (GLP-2) analog and a parenteral support (PS) for use in a method of treating short bowel syndrome (SBS) in a subject, the method comprising: administering the PS to the subject at a first volume and a first frequency, and measuring a baseline daily urine volume of the subject prior to administering the GLP-2 analog to the subject; administering the GLP-2 analog to the subject; measuring a produced daily urine volume of the subject following administration of the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume, thereby determining a daily urine production change; determining a modified volume and/or frequency of the PS, wherein: when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change; when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then: the modified volume and frequency of the PS equals the existing volume and frequency of the PS; the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS, optionally wherein the calorie content of the PS is increased or decreased; and administering the PS to the subject at the modified volume and/or frequency.

[0012] In some embodiments, administering the GLP-2 analog results in an improved function of the small intestine of the subject.

[0013] In some embodiments, the daily urine production change is an increase of daily urine production.

[0014] In some embodiments, the administering of the GLP-2 analog and modifying the volume and/or frequency of the PS steps are repeated for one or more times.

[0015] In some embodiments, the administering of the GLP-2 analog, determining a daily urine production change, determining a modified volume and/or frequency of PS, and administering the PS at the modified volume and/or frequency are repeated for one or more times.

[0016] In some embodiments, the subject is a CIC subject.

[0017] In some embodiments, the modified volume and/or frequency of the PS for the CIC subject is based on a medical condition of the CIC subject.

[0018] In some embodiments, the CIC subject demonstrates fluid overload, and the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS.

[0019] In some embodiments, the CIC subject demonstrates dehydration, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

[0020] In some embodiments, the CIC subject demonstrates acute renal failure, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

[0021] In some embodiments, the CIC subject demonstrates a stable medical condition, and the modified volume and/or frequency of the PS equals the existing volume and/or frequency of the PS.

[0022] In some embodiments, the PS comprises an intravenous infusion comprising fluid and/or nutrients. In some embodiments, the PS comprises fluid and electrolytes. In some embodiments, the PS further comprises a parenteral nutrition (PN). In some embodiments, the PN includes protein, carbohydrate, fat, vitamins, and/or trace elements.

[0023] In some embodiments, the subject is a CIC patient demonstrating calorie overload and the calorie content of the PN is decreased from baseline.

[0024] In some embodiments, the subject is a CIC patient demonstrating malnutrition and/or weight loss and the calorie content of the PN is increased.

[0025] In some embodiments, the use or the method further comprises determining the existing volume of PS per week.

[0026] In some embodiments, the GLP-2 analog is teduglutide, glepaglutide, apraglutide, elsiglutide, or a pharmaceutically acceptable salt thereof.

[0027] In some embodiments, the GLP-2 analog is apraglutide or a pharmaceutically acceptable salt thereof. In some embodiments, the apraglutide is a sodium salt of apraglutide.

[0028] In some embodiments, the apraglutide or pharmaceutically acceptable salt thereof is administered at a dose of about 2.5 mg/week of apraglutide when the subject has a body weight of less than 50 kg, or about 5 mg/week of apraglutide when the subject has a body weight greater than or equal to 50 kg.

[0029] In some embodiments, the apraglutide or pharmaceutically acceptable salt thereof is administered at a dose of about 1.5 mg/week of apraglutide when the subject has a body weight of less than 50 kg, or about 3.6 mg/week of apraglutide when the subject has a body weight greater than or equal to 50 kg.

[0030] In some embodiments, the GLP-2 analog is administered to the patient once weekly.

[0031] In some embodiments, the GLP-2 analog is administered twice weekly. In some embodiments, the GLP-2 analog is glepaglutide or a pharmaceutically acceptable salt thereof.

[0032] In some embodiments, the GLP-2 analog is administered daily. In some embodiments, the GLP-2 analog is teduglutide or a pharmaceutically acceptable salt thereof.

[0033] In some embodiments, the method further comprises administering the modified volume and/or frequency of the PS to the subject.

[0034] In some embodiments, the method further comprises measuring a baseline daily urine volume of the subject prior to administering the GLP-2 analog. In some embodiments, the PS volume administered to the subject has been optimized and stabilized prior to measuring the baseline daily urine volume and prior to administering the GLP-2 analog.

[0035] In some embodiments, the method further comprises determining the modified volume and/or frequency of the PS at 2, 3, 4, 5, 6 or 7 days after start of administering the GLP-2 analog.

[0036] In some embodiments, the method further comprises determining the modified volume and/or frequency of the PS at 1, 2, 3, 4, 5, 6, 7, 8, or more than 8 weeks after start of administering the GLP-2 analog. In some embodiments, the modified volume and/or frequency of the PS is determined weekly, biweekly, triweekly, or every four weeks. In some embodiments, the modified volume and/or frequency of the PS is determined every four weeks.

[0037] In some embodiments, the modified volume and/or frequency of the PS reduces risk of an adverse effect from administering the GLP-2 analog. In some embodiments, the adverse effect is fluid overload.

[0038] In another aspect, provided herein is *in vitro* method for determining a modified volume and/or frequency of parenteral support (PS) to be administered to a subject having short bowel syndrome (SBS) and who is receiving treatment with a glucagon-like peptide 2 (GLP-2) analog, comprising: measuring a baseline daily urine volume of the subject prior to

administration of the GLP-2 analog, wherein the subject has received an existing volume and frequency of PS; measuring a produced daily urine volume of the subject following administration of the GLP-2 analog; comparing the produced daily urine volume to the baseline daily urine volume, thereby determining a daily urine production change; and determining a modified volume and/or frequency of the PS, wherein when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change; when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS, optionally wherein the calorie content of the PS in is increased or decreased.

[0039] In some embodiments, the daily urine production change is an increase of daily urine production.

[0040] In some embodiments, the measuring the baseline daily urine volume, measuring the produced daily urine volume after administration of the GLP-2 analog, determining the daily urine production, and determining the modified volume and/or frequency of the PS are repeated for one or more times.

[0041] In some embodiments, the subject is a CIC subject.

[0042] In some embodiments, the modified volume and/or frequency of the PS for the CIC subject is based on a medical condition of the CIC subject.

[0043] In some embodiments, the CIC subject demonstrates fluid overload, and the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS.

[0044] In some embodiments, the CIC subject demonstrates dehydration, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

[0045] In some embodiments, the CIC subject demonstrates acute renal failure, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

[0046] In some embodiments, the CIC subject demonstrates a stable medical condition, and the modified volume and/or frequency of the PS equals the existing volume and/or frequency of the PS.

[0047] In some embodiments, the PS is an intravenous infusion comprising fluid and/or nutrients. In some embodiments, the PS comprises fluid and electrolytes. In some embodiments, the PS further comprises a parenteral nutrition (PN). In some embodiments, the PN comprises protein, carbohydrate, fat, vitamins, and/or trace elements.

[0048] In some embodiments, the subject is a CIC patient demonstrating calorie overload, and the calorie content of the PN is decreased from baseline.

[0049] In some embodiments, the subject is a CIC patient demonstrating malnutrition and/or weight loss, and the calorie content of the PN is increased.

[0050] In some embodiments, the GLP-2 analog is teduglutide, glepaglutide, apraglutide, or a pharmaceutically acceptable salt thereof.

[0051] In some embodiments, the GLP-2 analog is apraglutide or a pharmaceutically acceptable salt thereof. In some embodiments, the apraglutide is a sodium salt of apraglutide.

[0052] In some embodiments, the GLP-2 analog is glepaglutide or a pharmaceutically acceptable salt thereof.

[0053] In some embodiments, the GLP-2 analog is teduglutide or a pharmaceutically acceptable salt thereof.

[0054] In some embodiments, the modified volume and/or frequency of the PS is determined at 2, 3, 4, 5, 6 or 7 days after start of administering the GLP-2 analog.

[0055] In some embodiments, the modified volume and/or frequency of the PS is determined at 1, 2, 3, 4, 5, 6, 7, 8, or more than 8 weeks after start of administering the GLP-2 analog.

[0056] In some embodiments, the modified volume and/or frequency of the PS is determined weekly, biweekly, triweekly, or every four weeks.

[0057] In some embodiments, the modified volume and/or frequency of the PS is determined every four weeks.

DESCRIPTION OF THE DRAWINGS

[0058] FIG. 1 is a flow chart of optimization and stabilization periods of parenteral support (PS) for patients prior to receiving a GLP-2 analog. PS: parenteral support; OV: optimization visit; SV: stability visit; 48: 48-hours balance period prior to visit.

[0059] FIG. 2 is a schematic depiction of the PS volume algorithm described herein. PS: parenteral support; CIC: colon-in-continuity; AC: adjudication committee.

DETAILED DESCRIPTION

[0060] Short bowel syndrome (SBS) is a disabling malabsorptive disorder caused, for example, by extensive surgical bowel resection. Patients with extensive intestinal resections may suffer from disturbances in the gastrointestinal neuroendocrine feedback that regulate fluid and nutrient absorption. Disturbances include an impaired postprandial secretion of GLP-2, normally produced by L-cells in the terminal ileum and colon. Lack of GLP-2 might result in an accelerated gastrointestinal emptying, gastrointestinal hypersecretion, diminished intestinal blood flow, disturbed immunological and barrier function, and impaired mucosal growth. The consequent lack of intestinal adaptation contributes to the pathophysiological features of SBS, including frequent diarrheas or stoma emptying, malnutrition, dehydration, electrolyte imbalances and weight loss. SBS is also associated with significant morbidity and mortality, and an impaired quality of life. In patients with SBS and intestinal failure (SBS-IF), parenteral support (PS), comprising any combination of intravenous fluids and/or parenteral nutrition, is required to maintain health and/or growth. In contrast to patients with SBS-IF, patients with SBS intestinal insufficiency (SBS-II) manage without PS due to their ability to compensate for their malabsorption by hyperphagia, metabolic adjustments and/or by pharmacological treatments. However, patients with SBS-II may be at risk of fluid and electrolyte imbalances which necessitate repeated hospital admissions for PS administration. Collectively, patients with SBS have an impaired quality of life, significant morbidity and mortality, and are health care expensive.

[0061] While PS effectively saves a patient's life, the quality of life of these patients is impaired by the time they have to spend on PS, as well as the complications derived from the use of PS support, for example, catheter infections, hospitalizations and liver disease. Long-term PS provision may result in serious complications such as catheter-related blood stream infections (CRBSI) and intestinal failure-associated liver disease (IFALD). Thus, therapeutic goals of SBS-IF treatment include the reduction of the volume of PS across the patient spectrum: reduction in the time per day on PS; increasing the number of days off PS per week; or the ability to reach full oral/enteral autonomy.

[0062] As used herein, the term "amino acid" includes both naturally occurring amino acids and non-naturally occurring amino acids. Unless otherwise stated, an amino acid is an L-amino acid. Unless otherwise stated, amino acid sequences are presented from the N- terminus to the C-terminus.

[0063] As used herein, the term "control", when used alone or in reference to a quantity or

level, may refer to the level observed in a subject before administration of a treatment (*e.g.*, an effective dose of a GLP-2 analog), a level observed in a control subject or a population of subjects (including historically observed levels). When used in reference to a subject, a "control" may refer to the same subject before receiving a given treatment (*e.g.*, an effective dose of a GLP-2 analog), a similar subject who is not receiving any treatment for a given condition, or a similar subject who is receiving a treatment (*e.g.*, surgery, wound care, and/or nutritional support) that does not comprise the given treatment (*e.g.*, administration of an effective dose of a GLP-2 analog).

[0064] As used herein, "enteral autonomy" refers to a subject not receiving parenteral support for hydration or parenteral nutrition for calories.

[0065] 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 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. An exemplary amino acid sequence of naturally-occurring GLP-2 is set forth in SEQ ID NO:1. GLP-2 analogs are known in the art and can include, for example and without limitation, glepaglutide, NM-003, teduglutide, apraglutide, and elsiglutide, and pharmaceutically acceptable salts thereof.

[0066] As used herein, the terms "patient" and "subject" are used interchangeably and refer to any subject for whom therapy is desired. In some embodiments, the subject is a mammal, *e.g.*, a human or a non-human mammal. In some embodiments, the subject is a human.

[0067] As used herein, the term "treatment" (also "treat" or "treating") refers to any administration of a therapeutic entity (*e.g.*, a therapeutic compound or composition as described herein) that partially or completely reduces the need for parenteral support.

[0068] As used herein, the term "parenteral support" or "PS" refers to the provision of fluids and/or nutrients (*e.g.*, electrolytes) to a subject receiving a GLP-2 analog as a means of providing the subject with necessary fluid and/or nutrients, when such subjects are unable to absorb due to their condition (*e.g.*, SBS). PS may be an intravenous infusion or other suitable means of administration. In some embodiments, PS includes "parenteral nutrition" or "PN" which may include protein, carbohydrate, fat, vitamins, and/or trace elements. In some embodiments, PN, and thus PS, provides calories to a subject in need thereof, *e.g.*, a subject

demonstrating malnutrition and/or weight loss. In some embodiments, PN, and thus PS, is reduced in a subject in need of reduced caloric intake, *e.g.*, a subject demonstrating a calorie overload. In some embodiments, a subject receiving PS refers to any patient indicated for, prescribed, or administered PS.

[0069] As used herein, the term "purity" is used to refer to purity as determined by chromatographic methods, more specifically by Ultra Performance Liquid Chromatography (UPLC) methods and/or High-Performance Liquid Chromatography (HPLC) methods.

[0070] Any one of the embodiments and/or aspects described herein can be combined with any other embodiment and/or aspect described herein, and any number of embodiments and/or aspects can be combined.

GLP-2 Analogs

[0071] After surgical resection, the remnant bowel may undergo structural and functional changes to increase its absorptive capacity (commonly referred to as intestinal adaptation). The secretion of neuroendocrine peptides throughout the gastrointestinal tract contribute to this adaptation. The pathophysiological traits of SBS are often caused by disturbance in the neuroendocrine feedback mechanisms and lack of intestinal adaptation. This includes an impaired postprandial secretion of glucagon-like peptide-2 (GLP-2) which is produced by intestinal L-cells predominantly located in the terminal ileum and proximal colon.

[0072] Native GLP-2 has a short circulating half-life due to cleavage by dipeptidyl peptidase-IV (DPP4). Apraglutide is a next generation synthetically manufactured GLP-2 analog with a molecular structure designed to provide long-lasting constant exposure and an increased half-life to at least 30 hours as compared with human GLP-2 and other GLP-2 analogs. Apraglutide differs from human GLP-2 by four amino acid substitutions and was identified through chemistry structure-activity relationship studies of lipophilic amino acid substitutions in positions 11 and 16 of [Gly2] hGLP-2 (1-33). In animal models, apraglutide promoted increase in intestinal length and weight, villus height and crypt depth. Pharmacokinetic (PK) and pharmacodynamic studies in animals have suggested that apraglutide may have a low clearance, long elimination half-life and a high plasma protein binding compared with other GLP-2 analogs. Therefore, apraglutide provides a once weekly dosing regimen. Apraglutide treatment can potentially help patients to regain enteral autonomy or reduce PS requirements, improve symptoms of malabsorption, alleviate organ failures secondary to II and IF, and prevent patients with SBS-II from deteriorating into a situation of intermittent or chronic IF.

[0073] GLP-2 analogs that can be used in methods of the present disclosure include, for example, those disclosed in International Patent Application No. WO 2006/117565 and US Pat. 8,589,918, the entire contents of each which are herein incorporated by reference. The GLP-2 analog apraglutide and related compounds (*see*, *e.g.*, US Pat. No. 8,589,918) have superior pharmacokinetic properties and are contemplated for use in the present methods.

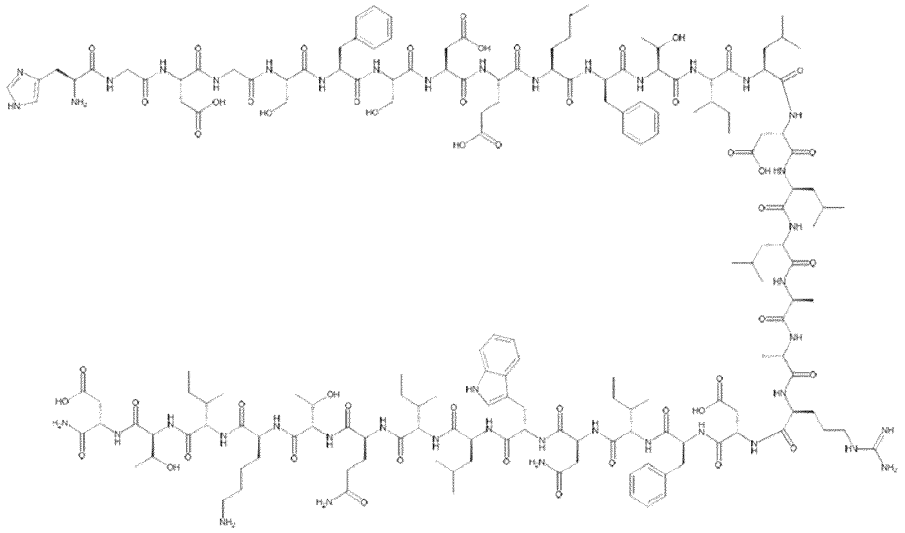
SEQ ID NO: 1 (GLP-2) His-Ala-Asp-Gly-Ser-Phe-Ser-Asp-Glu-Met-Asn-Thr-Ile-Leu-Asp-Asn-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Asn-Trp-Leu-Ile-Gln-Thr-Lys-Ile-Thr-Asp-OH

SEQ ID NO: 2 (Apraglutide) 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-NH_2

[0074] In some embodiments, the GLP-2 analog is apraglutide, a peptide having the amino acid sequence of SEQ ID NO: 2, where Nle is norleucine and D-Phe is the D-amino acid phenylalanine.

[0075] In some embodiments, the GLP-2 analog is a pharmaceutically acceptable salt of apraglutide. In some embodiments, the GLP-2 analog is a sodium salt of apraglutide.

[0076] In some embodiments, the apraglutide has the following structure:



[0077] Methods of making apraglutide, and pharmaceutically acceptable salts thereof, are described, for example, in WO 2021/252659, herein incorporated by reference in its entirety.

[0078] In some embodiments, the apraglutide, or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, has a purity of no less than 94%. In some embodiments, the apraglutide, or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, has a purity of no less than 95%. In some embodiments, the apraglutide, or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, has a purity of no less than 97%. In some embodiments, the apraglutide, or a salt thereof, does not contain any unspecified impurity at a concentration greater than 0.01%, 0.05%, 0.1%, 0.5%, 1%, 1.5%, or 2%. In some embodiments, the apraglutide, or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, does not contain any unspecified impurity at a concentration greater than 1%.

Formulation

[0079] GLP-2 analogs of the present disclosure can use used alone as a pharmaceutical or in a pharmaceutical composition comprising one or more GLP-2 analogs as the active ingredient(s) and a pharmaceutically acceptable adjuvant, excipient, diluent, or carrier. Pharmaceutical compositions may also comprise other active ingredients.

[0080] Suitable pharmaceutically acceptable carriers include those typically used with peptide-based drugs. *See*, *e.g.*, "Remington: The Science and Practice of Pharmacy," 22nd ed., Pharmaceutical Press, Philadelphia, PA, 2012, for general guidance on drug formulations. Non-limiting examples of suitable excipients include glycine, L-histidine, mannitol, and any combination thereof.

[0081] An exemplary formulation uses glycine as a buffering agent. L-Histidine is used in this formulation as a physically stabilizing agent. L-Histidine also serves as a buffer, maintaining the target pH. Mannitol is used in this formulation as a bulking agent in the lyophilization process step. Water for injection is the solvent of this formulation; the water for injection is removed during the lyophilization step. Sodium hydroxide is used for pH adjustment of the pre-lyophilization solution. pH is measured and may be adjusted to 8.30 ± 0.10 or 8.30 ± 0.20 with sodium hydroxide (NaOH) solution.

[0082] In some embodiments, the GLP-2 analog, *e.g.*, apraglutide or a pharmaceutically acceptable salt thereof, *e.g.*, the sodium salt thereof, is formulated for injection. A first exemplary, non-limiting formulation of apraglutide is described in Table 1 below. A second exemplary, non-limiting formulation of apraglutide is described in Table 2 below.

Table 1. First example formulation of apraglutide for injection.

Name of Ingredient	Reference	Function	Quantity	
			Apraglutide formulation (mg/vial)	Reconstituted Solution (mg/mL)
Apraglutide (free acid)	In-house	Drug substance	12.5[a]	25
Glycine	Ph. Eur/USP	Buffering Agent	1.88	3.75
L-Histidine	Ph. Eur/USP	Stabilizing Agent	3.88	7.75
Mannitol	Ph. Eur/USP	Bulking Agent	57.5	115.0
Sodium Hydroxide	Ph. Eur/USP	pH adjustment	q.s. to pH 8.3	--
Water for Injection (WFT)[b]	Ph. Eur/USP	Solvent	1.25 ml	--
Nitrogen[b]	NF	Inert Overlay	--	--
Sterile Water for Injection	Ph. Eur/USP	Reconstitution diluent	--	0.5 mL

[a] The quantity of drug substance to be used is calculate based on the apraglutide content in the corresponding drug substance batch.
[b] Components used during the manufacture of the drug product that do not appear in the final product.

Table 2. Additional exemplary pharmaceutical compositions comprising apraglutide.

Component	Function	5.2 mg/vial		10.4 mg/vial		Pre-lyophilization Solution (mg/mL)
		Quantity (mg/vial)	Reconstituted Solution (mg/mL)[a]	Quantity (mg/vial)	Reconstituted Solution (mg/mL)[a]	
Apraglutide (Free acid)	Drug substance	5.20[b]	21	10.4[b]	21	10.0
Glycine	Buffering agent	0.78	3.1	1.56	3.2	1.50
L-Histidine	Stabilizing agent	1.61	6.4	3.22	6.5	3.10
Mannitol	Bulking agent	23.92	95	47.84	97	46.0
Sodium Hydroxide	pH adjustment	q.s. to pH 8.3	--	q.s. to pH 8.3	--	q.s. to pH 8.3
Sterile water[c]	Solvent	q.s. to 0.52 mL	--	q.s. to 1.04 mL	--	
Nitrogen[d]	Processing aid	--	--	--	--	
Sterile water for injection	Reconstitution diluent	--	0.23 mL	--	0.45 mL	

[a] Reconstituted concentration based on a displacement volume of 0.69 mL/g of cake.

[b] The quantity of drug substance to be used is calculated based on the apraglutide content in the corresponding drug substance batch.
[c] Component used during the manufacture that does not appear in the final product.
[d] Used as inert overlay in the finished product.

[0083] In some embodiments, the apraglutide composition may include one or more excipients comprising glycine, L-histidine, mannitol, water for injection (WFI), sterile water for injection (sWFI), sodium hydroxide, sucrose, or any combination thereof.

[0084] In some aspects, the present disclosure provides a pharmaceutical composition which is an aqueous solution for lyophilization (*i.e.*, a pre-lyophilization solution) 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.

[0085] In some aspects, the present disclosure provides a pharmaceutical composition comprising apraglutide of the present disclosure, glycine, L-histidine and mannitol, optionally 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 is a lyophilized cake. In some embodiments, the preceding pharmaceutical composition is an aqueous solution and can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[0086] 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 is a lyophilized cake. In some embodiments, the preceding pharmaceutical composition is an aqueous solution and can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[0087] 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 is a lyophilized cake. In some embodiments, the preceding pharmaceutical composition is an aqueous solution and can further comprise sodium hydroxide in an amount such that the pH of the solution is about pH 8.3.

[0088] 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.

[0089] 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.

[0090] In some embodiments, the pharmaceutical composition comprises about 10.0 mg/ml of apraglutide free acid, about 1.50 mg/ml of glycine, about 3.10 mg/ml of L-histidine, about 46.0 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.

[0091] 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.

[0092] The GLP-2 analog peptide composition for injection may be an aseptically manufactured lyophilized powder which can be reconstituted with sterile water 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 sterile Water for Injection (sWFI). The reconstituted solution may be administered subcutaneously.

Administration

[0093] In some embodiments, GLP-2 analogs, *e.g.*, apraglutide, are 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 for example and without limitation, water, saline, aqueous dextrose and glycols.

Dosing

[0094] Amounts that constitute an effective dose may depend on various factors such as the disease and clinical status of the patient (*e.g.*, weight), the route of administration and the GLP-2 analog used. Doses may be administered, *e.g.*, twice daily, once daily, twice a week, weekly, biweekly, once or twice monthly, *etc.* Doses generally range from about 1 mg to about 30 mg per week for a period of about 1 week to about 100 weeks. In some embodiments, the GLP-2 analog is apraglutide or a pharmaceutically acceptable salt thereof, and the weekly dose is between about 1 mg and 10 mg. In some embodiments, the GLP-2 analog is glepaglutide or a pharmaceutically acceptable salt thereof, and the weekly dose is between about 1 mg and 20 mg. In some embodiments, 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 2 weeks to about 24 weeks, about 2 weeks to about 20 weeks, or about 2 weeks to about 16 weeks. In some embodiments, subjects are administered a dose about once a week. In some embodiments, subjects are administered a dose about once every two weeks or about twice a month.

[0095] Administration of a GLP-2 analog, such as apraglutide, increases citrulline levels in a dose dependent manner. Citrulline is a marker of small bowel enterocyte mass. Dosing of apraglutide at about 1 mg to about 10 mg, or any range therebetween, induces long-lasting increases in citrulline concentration in patients. Dosing of apraglutide at about 1 mg, about 1.5 mg, about 2.5 mg, about 3.6 mg, about 5 mg, and about 10 mg induces long-lasting increases in citrulline concentration in patients.

[0096] In some embodiments, apraglutide is administered parenterally (*e.g.*, subcutaneously, intravenously, intramuscularly, or orally). In some embodiments, apraglutide is administered intravenously. In some embodiments, apraglutide is administered subcutaneously.

[0097] 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 2.5 mg of apraglutide to prevent high exposures. Patients of 50 kg or higher may receive 5 mg of apraglutide or higher doses. Alternatively, it is desired to dose patients with body weight below 50 kg with 1.5 mg of apraglutide to prevent high exposures. Patients of 50 kg or higher may receive 3.6 mg of apraglutide or higher doses.

Parenteral Support

[0098] The large degree of heterogeneity across the SBS-IF severity spectrum is a challenge in clinical trials with GLP-2 analogs. Patients with SBS-IF and CIC may require a different weaning approach than SBS-IF patients with stoma. Accordingly, in some aspects, the present disclosure provides a PS volume reduction algorithm for all subjects (*i.e.*, both stoma and CIC) based on fluid balance. CIC patients who do not reach the threshold for change in urinary output at trial visits compared to baseline will follow a different process based on a combination of clinical factor evaluations instead of a single physiological parameter. In some embodiments, these clinical factors are evaluated by the patient's physician. In some embodiments, these clinical factors are evaluated by an adjudication committee. In some embodiments, an adjudication committee comprised of medical investigators who evaluate various physiological parameters for the CIC subjects.

[0099] In a previous 24-week treatment phase 3 trial with the GLP-2 analog teduglutide, PS volume could be reduced by 10% at clinical visits, if urinary output increased by at least 10% (Jeppesen *et al.* (2011), *Gut*; 60:902-914). Many subjects in this trial suffered from fluid overload and stopped drinking. In a follow-up phase 3 trial (STEPS trial) PS volume reductions of at least 10%, but not more than 30%, were allowed if urinary output increased by at least 10% (Jeppesen *et al.* (2012), *Gastroenterology*; 143:1473-1481), However, in this trial some subjects also suffered from fluid overload. These fluid overloads were the result of strong drug effects on intestinal absorption that cannot be followed by adequate reductions in PS volume.

[00100] Accordingly, in some aspects, the present disclosure provides a PS optimization phase and stability or stabilization phase prior to treatment with a GLP-2 analog, which aims to establish the subjects' stable volume of PS. A non-limiting, exemplary optimization phase and stabilization phase is disclosed in Example 1 for apraglutide and depicted in **FIG. 1**.

[00101] In some aspects, provided herein is a GLP-2 analog (*e.g.*, apraglutide) for use in a method of treating SBS in a subject receiving a PS, the method comprising administering the GLP-2 analog to the subject receiving an existing volume and frequency of the PS for a period

of time (*e.g.*, a volume of PS after optimization and stabilization); and modifying the volume and/or frequency of the PS, comprising measuring a produced daily urine volume of the subject upon administering the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume prior to treatment with a GLP-2 analog, thereby determining a daily urine production change; and determining a modified volume and/or frequency of the PS, wherein when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change; when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS. In some embodiments, if a CIC subject exhibits weight gain due to edema (*i.e.*, fluid overload), the volume of the PS is reduced with or without reduction of the calorie content of the PS. In some embodiments, if a CIC subject exhibits weight gain without edema, the calorie content of the PS is reduced. In some embodiments, if a CIC subject exhibits weight loss and is dehydrated, the volume of the PS should be increased with or without an increase in calorie content of the PS. In some embodiments, if a CIC subject exhibits weight loss without dehydration, the calorie content of the PS is increased. The GLP-2 analog for use as described herein thus stratifies stoma subjects and CIC subjects, recognizing the spectrum of SBS patients and needs of the groups as described herein.

[00102] In some aspects, provided herein is a method of treating SBS in a subject receiving a PS, the method comprising administering a glucagon-like peptide 2 (GLP-2) analog (*e.g.*, apraglutide, teduglutide, or glepaglutide) to the subject receiving an existing volume and frequency of the PS for a period of time; and modifying the volume and/or frequency of the PS, comprising measuring a produced daily urine volume of the subject upon administering the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume, thereby determining a daily urine production change; and determining a modified volume and/or frequency of the PS, wherein when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change; when the daily

urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS In some embodiments, if a CIC subject exhibits weight gain due to edema (*i.e.*, fluid overload), the volume of the PS is reduced with or without reduction of the calorie content of the PS. In some embodiments, if a CIC subject exhibits weight gain without edema, the calorie content of the PS is reduced. In some embodiments, if a CIC subject exhibits weight loss and is dehydrated, the volume of the PS should be increased with or without an increase in calorie content of the PS. In some embodiments, if a CIC subject exhibits weight loss without dehydration, the calorie content of the PS is increased.

[00103] In some embodiments, administering the GLP-2 analog (*e.g.*, apraglutide) results in an improved function of the small intestine of the subject. In some embodiments, improved function of the small intestine results in one or more of: an increase in the intestinal absorption of dietary intake wet weight of the subject; a decrease in the fecal output of the subject; an increase in the absolute urine volume output of the subject; an increase in the intestinal absorption of sodium and potassium of the subject; an increase in the sodium and potassium urine excretion of the subject; an increase in the intestinal absorption of energy of the subject; a decrease in the energy content of fecal output of the subject; and an increase in the plasma citrulline concentration of the subject.

[00104] In some embodiments, the methods of the disclosure facilitate early assessment of a changed PS volume need (*e.g.*, within a few days of initiating GLP-2 analog therapy, or when improved physiological function occurs). In some embodiments, the methods provide an algorithm for adjusting of PS volume during a course of GLP-2 therapy, *e.g.*, apraglutide. Those of skill in the art will readily appreciate the use of the algorithm disclosed herein to adjust the PS volume provides an adjustment of the PS volume that is patient-dependent.

[00105] "Baseline daily urine volume" as used herein refers to a daily urine production which is taken prior to treatment with a GLP-2 analog. For example, a baseline daily urine volume may be measured after a subject's volume of PS has been optimized and stabilized, but before treatment with a GLP-2 analog, *e.g.*, a GLP-2 analog as described herein. For example, prior to treatment with a GLP-2 analog, a subject collects urine for a 48-hour period when oral fluid

intake of the subject is kept constant. The collected volume of urine is then divided by 2 to obtain the baseline daily urine volume. Baseline daily urine may be provided in L/day.

[00106] "Daily urine production" or "produced daily urine volume" refers to the daily average urine produced by a subject when oral fluid intake is kept constant during the period when urine is collected. For example, urine is collected for a 48-hour period when oral fluid intake of the subject is kept constant. The collected volume of urine is then divided by 2 to obtain the daily urine production. The daily urine volume measurement is obtained prior to a determination of PS volume adjustment. As described herein, average daily urine production minus baseline daily urine volume provides a daily urine production change. In some embodiments, the threshold of daily urine production change for determining a change in PS volume is about 10% or higher. In some embodiments, the threshold of daily urine production change for determining a change in PS volume is about 5% or higher, dependent on the subject's medical condition. In some embodiments, a change in PS is based on the recommendation of a medical provider, dependent on the subject's medical condition. In some embodiments, produced daily urine volume is measured upon administering the GLP-2 analog, *i.e.*, the volume of urine produced in the 48 hours immediately following the GLP-2 analog administration, divided by 2.

[00107] "Baseline PS" as used herein refers to the PS administered in the week prior to the first PS volume adjustment determination. In some embodiments, baseline PS is determined after an optimization and stabilization period. Baseline PS may be provided as volume in L/week.

[00108] In some aspects, provided herein is method for adjusting a parenteral support (PS) volume in a subject receiving a volume of parenteral support each week, the method comprising calculating a new PS volume using an algorithm in which a weekly PS volume is calculated by subtracting seven times the absolute increase in daily urine volume from a baseline PS volume, *i.e.*, PS volume at the initiation of GLP-2 therapy, from the current weekly volume of PS, thereby providing a new weekly PS volume for the subject. Thus, the new PS weekly volume for the subject equals the current PS weekly volume minus seven times (7×) the absolute increase in daily urine volume from the baseline daily urine volume.

[00109] In some embodiments, PS is adjusted (*i.e.*, reduced) if the daily urine volume is at least 10% higher than baseline urine volume. In some embodiments, the method comprises determining the current PS volume (weekly) for use determining the reduced PS volume using the algorithm.

[00110] In some embodiments, when the daily average urine volume of the balance period prior to the current visit is less than 10% higher than baseline value, PS volume is determined by whether the subject has stoma or CIC. In some embodiments, when the subject has stoma, the PS volume will not be changed. In some embodiments, when the subject has CIC, clinical evaluation (*e.g.*, by the subject's doctor or by an independent committee such as an adjudication committee) determines PS volume. In some embodiments, if a CIC subject exhibits weight gain due to edema (*i.e.*, fluid overload), the volume of the PS is reduced with or without reduction of the calorie content of the PS. In some embodiments, if a CIC subject exhibits weight gain without edema, the calorie content of the PS is reduced. In some embodiments, if a CIC subject exhibits weight loss and is dehydrated, the volume of the PS should be increased with or without an increase in calorie content of the PS. In some embodiments, if a CIC subject exhibits weight loss without dehydration, the calorie content of the PS is increased.

[00111] In some embodiments, when the subject is a CIC subject, the urinary output driven algorithm comprises a clinical assessment of the subject with CIC. In some embodiments, the clinical assessment comprises body weight, stools (consistency, frequency, *etc.*), a physician narrative of the overall well-being, change in eating/appetite, fluid intake (oral drinking volume and PS), and/or daily urinary volume from 48-hour balance period which may lead to further reduction in PS.

[00112] In some embodiments, PS is reduced in volume. In some embodiments, PS is reduced in frequency of administration. As would be readily appreciated by one of skill in the art, a reduction of weekly PS volume may result in a reduction of PS frequency.

[00113] By way of illustration of the above, in a non-limiting example, a subject is receiving 12 L PS/week, receiving PS 4 times/week (*i.e.*, 3 L on average for 3 days). When daily urinary volume is increased by 500 mL, weekly PS volume is reduced by 3.5L. As the subject receives 3 L PS, which is less than 3.5 L, the subject receives a day less of PS. Such subject will receive 3 L PS, 3 times a week, moving forward.

[00114] In some embodiments, PS volume is reduced by no more than 50%, *e.g.*, about 40%, about 30%, about 20%, about 10%, about 5%, or less than 5%.

[00115] In some embodiments, the method further comprises the step of administering the reduced PS volume to the subject. In some embodiments, the method is repeated, for example every week, month, or at physician visits, facilitating the PS volume to be reduced in response to the subject demonstrating continued improved function of the small intestine. In some embodiments, the PS is determined 2, 3, 4, 5, 6 or 7 days after start of administering the GLP-2 analog, *e.g.*, apraglutide. In some embodiments, the PS is determined 1, 2, 3, 4, 5, 6, 7, 8, or

more than 8 weeks after start of administering the GLP-2 analog, *e.g.*, apraglutide. In some embodiments, the PS is determined weekly, biweekly, triweekly, or every four weeks.

[00116] In some embodiments, PS adjustment results in target urine volume of at least 800 ml/day, and less than 2.5 L/day, *e.g.*, about 800 ml/day, about 1000 ml/day, about 1200 ml/day, about 1500 ml/day, about 2 L/day, or about 2.5 L/day.

[00117] In some embodiments, the method comprises determining the baseline volume of urine. In some embodiments, the method comprises determining the daily urine volume. Some or all the steps of the method may be repeated during the course of the GLP-2 therapy received by the subject or as needed. It is contemplated herein that as the absorptive capacity of the intestines increases after treatment with the GLP-2 analog, *e.g.*, apraglutide, PS volume will decrease to avoid fluid overload. In addition, GLP-2 analogs may increase calorie absorption in a subject, which may result in decrease in calorie content of the subjects PS. As described herein, decreasing PS improves quality of life for the patient.

Indications

[00118] In some embodiments, a subject who has been administered an effective dose of a GLP-2 analog needs less nutritional support relative to a control. For example, and without limitation, a subject who has been administered an effective dose of GLP-2 analog needs at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% less nutritional support relative to a control. In some embodiments, a subject who has been administered an effective dose of a GLP-2 analog needs 100% less nutritional support relative to a control (*i.e.*, enteral autonomy).

[00119] In some embodiments, a subject who has been administered an effective dose of a GLP-2 analog needs total parenteral support for fewer days relative to a control. For example, in some embodiments, administration of an effective dose of a GLP-2 analog may reduce the length of time during which total parenteral support is needed by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% relative to a control. In one embodiment, administration of an effective dose of GLP-2 analog reduces the length of time during which total parenteral support is needed by 100% relative to a control (*i.e.*, enteral autonomy). In some embodiments, a subject who has been administered an effective dose of a GLP- 2 analog needs total parenteral support for less than 85 days per year, less than 80 days per year, less than 75 days per year, less than 70 days per year, less than

65 days per year, less than 60 days per year, less than 55 days per year, less than 50 days per year, less than 45 days per year, less than 40 days per year, less than 35 days per year, less than 30 days per year, less than 25 days per year, less than 20 days per year, less than 15 days per year, less than 10 days per year, or less than 5 days per year.

[00120] In some embodiments, a subject who is administered an effective dose of a GLP-2 (*e.g.*, apraglutide) analog does not need total parenteral nutrition following treatment.

[00121] In some embodiments, the patients receiving apraglutide include male and female subjects with short bowel syndrome associated intestinal failure ("SBS-IF"), receiving parenteral support, secondary to surgical resection of the small intestine with either:

a. Colon-in-continuity ("CIC") remaining and no stoma (small intestine <200 cm from duodeno-jejunal flexure, based on available medical/surgical records) with the latest intestinal resection being at least 12 months prior to screening OR

b. Jejunostomy or ileostomy (<200 cm from duodeno-jejunal flexure, based on available medical/surgical records) with the latest intestinal resection being at least 6 months prior to screening.

[00122] In some embodiments, the subject is a colon-in-continuity subject, or a CIC subject. As used herein, "colon-in-continuity" or "CIC" subjects refer to patients retaining all, or part, of the colon and the jejunum or ileum has been anastomosed to the remaining colon. In some embodiments, such patients require moderate to low PS volume, *e.g.*, a minimum volume required to deliver calories needed. Such patients generally have a higher likelihood of achieving enteral autonomy during treatment.

[00123] In some embodiments, the subject is a stoma subject. As used herein, a "stoma subject" generally refers to patients with jejunostomies or ileostomies, and no CIC. In some embodiments, such patients have higher PS volume requirements, driven by a large volume of fluids and electrolytes. Such patients generally have a lower likelihood of achieving enteral autonomy during treatment.

[00124] In some embodiments, administration of an effective dose of a GLP-2 analog results in reduced hospital length of stay relative to a control. For example, in some embodiments, administration of an effective dose of a GLP-2 analog (*e.g.*, apraglutide) may reduce the length of a hospital stay by at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% relative to a control. In some embodiments, a subject who has been administered an effective dose of a GLP-2 analog is hospitalized for less

than 50 days, less than 45 days, less than 40 days, less than 35 days, less than 30 days, less than 25 days, less than 20 days, less than 15 days, less than 10 days, or less than 5 days.

[00125] In some embodiments, administration of an effective dose of a GLP-2 analog to a population of subjects reduces the mortality rate relative to a population of subjects who receive a standard of care treatment (*e.g.*, surgical treatment, nutritional support, and wound care) that does not comprise administration of an effective dose of a GLP-2 analog. For example, in some embodiments, the mortality rate is reduced to less than 15%, less than 12%, less than 10%, less than 8%, less than 5%, less than 3%, less than 2%, or less than 1%. The SC injection will typically be administered in the abdominal area or in the thigh. Generally, the injection site should be rotated such that an injection is administered at least 5 cm away from where the last injection was administered.

[00126] In some embodiments, a single 2.5 mg dose (for subjects with body weight less than 50 kg at most recent trial visit) or 5 mg dose (for subjects with body weight 50 kg or more at most recent trial visit) of apraglutide or matching placebo will be administered by subcutaneous ("SC") injection once weekly during a treatment period of 24 weeks (stoma) or 48 weeks (CIC).

[00127] In some embodiments, a single 1.5 mg dose (for subjects with body weight less than 50 kg at most recent trial visit) or 3.6 mg dose (for subjects with body weight 50 kg or more at most recent trial visit) of apraglutide or matching placebo will be administered by subcutaneous ("SC") injection once weekly during a treatment period of 24 weeks (stoma) or 48 weeks (CIC).

[00128] Any use of growth hormone, glutamine or growth factors such as native GLP-2, GLP-1 or GLP-2, GLP-1 analogs other than the IMP under investigation should be discontinued for 12 month (CIC subjects) and 6 months (stoma subjects) before administration of the apraglutide.

[00129] In some embodiments, administration of an effective dose of a GLP-2 analog to a population of subjects reduces the morbidity rate relative to a population of subjects who receive a standard of care treatment (*e.g.*, surgical treatment, nutritional support, and wound care) that does not comprise administration of an effective dose of a GLP-2 analog. For example, in some embodiments, the morbidity rate is reduced to less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, or less than 10%.

[00130] In some embodiments, apraglutide is used for post-surgical enteral autonomy recovery or for treatment of enterocutaneous fistulas. In some embodiments, apraglutide is used for treatment of anastomotic leaks, functional intestinal failure, intestinal insufficiency, necrotizing enterocolitis, graft versus host disease, Crohn's disease or celiac disease.

[00131] In some aspects, the present disclosure provides a method of treating short bowel syndrome in a subject, the method comprising administering at least one therapeutically effective amount of a GLP-2 analog peptide (*e.g.*, apraglutide).

[00132] In some aspects, the present disclosure provides a GLP-2 analog peptide (*e.g.*, apraglutide) of the present disclosure for use in the treatment of short bowel syndrome in a subject, wherein the GLP-2 analog peptide of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00133] In some aspects, the present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for the manufacture of a medicament for treating of short bowel syndrome in a subject, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00134] In some aspects, the present disclosure provides a method for increasing the intestinal absorption of wet weight in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing the intestinal absorption of wet weight in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing the intestinal absorption of wet weight in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00135] In some aspects, the increase in intestinal absorption of wet weight can be at least about 100 g/day, or at least about 200 g/day, or at least about 300 g/day, or at least about 400 g/day, or at least about 500 g/day, or at least about 600 g/day, or at least about 700 g/day, or at least about 800 g/day, or at least about 900 g/day, or at least about 1000 g/day.

[00136] In some aspects, the present disclosure provides a method for decreasing fecal output in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a method for decreasing stoma output in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of decreasing the fecal output in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for decreasing the fecal output in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00137] In some aspects, the decrease in fecal output can be at least about 100 g/day, or at least about 200 g/day, or at least about 300 g/day, or at least about 400 g/day, or at least about 500 g/day, or at least about 600 g/day, or at least about 700 g/day, or at least about 800 g/day, or at least about 900 g/day, or at least about 1000 g/day.

[00138] In some aspects, the present disclosure provides a method for increasing urine production in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing the urine production in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing the urine production in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00139] In some aspects, the increase in urine production can be at least about 100 g/day, or at least about 200 g/day, or at least about 300 g/day, or at least about 400 g/day, or at least about

500 g/day, or at least about 600 g/day, or at least about 700 g/day, or at least about 800 g/day, or at least about 900 g/day, or at least about 1000 g/day.

[00140] In some aspects, the present disclosure provides a method for increasing absorption of sodium and/or potassium in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing the absorption of sodium and/or potassium in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing the absorption of sodium and/or potassium in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00141] In some aspects, the increase in absorption of sodium and/or potassium can be at least about 5 mmol/day, or at least about 10 mmol/day, or at least about 15 mmol/day, or at least about 20 mmol/day, or at least about 25 mmol/day, or at least about 30 mmol/day, or at least about 35 mmol/day, or at least about 40 mmol/day, or at least about 45 mmol/day, or at least about 50 mmol/day.

[00142] In some aspects, the present disclosure provides a method for increasing urine sodium and/or potassium excretion in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing the urine sodium and/or potassium excretion in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing the urine sodium and/or potassium excretion in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00143] In some aspects, the increase urine sodium and/or potassium excretion can be at least about 5 mmol/day, or at least about 10 mmol/day, or at least about 15 mmol/day, or at least about 20 mmol/day, or at least about 25 mmol/day, or at least about 30 mmol/day, or at least about 35 mmol/day, or at least about 40 mmol/day, or at least about 45 mmol/day, or at least about 50 mmol/day.

[00144] In some aspects, the present disclosure provides a method for increasing intestinal absorption of energy in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing the intestinal absorption of energy in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing the intestinal absorption of energy in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00145] In some aspects, the increase intestinal absorption of energy can be at least about 500 kJ/day, or at least about 600 kJ/day, or at least about 700 kJ/day, or at least about 800 kJ/day, or at least about 900 kJ/day, or at least about 1000 kJ/day, or at least about 1100 kJ/day or at least about 1200 kJ/day.

[00146] In some aspects, the present disclosure provides a method for decreasing the energy content of fecal output in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of decreasing the energy content of fecal output in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for decreasing the energy content of fecal output in a subject with short bowel syndrome, wherein the GLP-2 analog peptide

composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00147] In some aspects, the decrease in the energy content of the fecal output can be at least about 500 kJ/day, or at least about 600 kJ/day, or at least about 700 kJ/day, or at least about 800 kJ/day, or at least about 900 kJ/day, or at least about 1000 kJ/day, or at least about 1100 kJ/day or at least about 1200 kJ/day.

[00148] In some aspects, the present disclosure provides a method for increasing carbohydrate and/or lipid absorption in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing carbohydrate and/or lipid absorption in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing carbohydrate and/or lipid absorption in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00149] In some aspects, the increase in carbohydrate and/or lipid absorption can be at least about 100 kJ/day, or at least about 200 kJ/day, or at least about 300 kJ/day, or at least about 400 kJ/day, or at least about 500 kJ/day, or at least about 600 kJ/day, or at least about 700 kJ/day, or at least about 800 kJ/day, or at least about 900 kJ/day, or at least about 1000 kJ/day, or at least about 1100 kJ/day or at least about 1200 kJ/day.

[00150] In some aspects, the present disclosure provides a method for increasing protein absorption in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing protein absorption in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing protein absorption in a subject with short bowel syndrome,

wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00151] In some aspects, the increase in protein absorption can be at least about 100 kJ/day, or at least about 200 kJ/day, or at least about 300 kJ/day, or at least about 400 kJ/day, or at least about 500 kJ/day, or at least about 600 kJ/day, or at least about 700 kJ/day, or at least about 800 kJ/day, or at least about 900 kJ/day, or at least about 1000 kJ/day, or at least about 1100 kJ/day or at least about 1200 kJ/day.

[00152] In some aspects, the present disclosure provides a method for increasing body weight in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure for use in a method of increasing body weight in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing body weight in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00153] In some aspects, the increase in body weight can be at least about 0.5 kg, or at least about 1.0 kg, or at least about 1.5 kg, or at least about 2.0 kg, or at least about 2.5 kg, or at least about 3.0 kg, or at least about 3.5 kg, or at least about 4.0 kg, or at least about 4.5 kg, or at least about 5.0 kg.

[00154] In some aspects, the present disclosure provides a method for increasing lean body mass in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing lean body mass in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing lean body mass in a subject with short bowel syndrome, wherein

the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00155] In some aspects, the increase in lean body mass can be at least about 0.5 kg, or at least about 1.0 kg, or at least about 1.5 kg, or at least about 2.0 kg, or at least about 2.5 kg, or at least about 3.0 kg, or at least about 3.5 kg, or at least about 4.0 kg, or at least about 4.5 kg, or at least about 5.0 kg.

[00156] In some aspects, the present disclosure provides a method for decreasing fat mass in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of decreasing fat mass in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for decreasing fat mass in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00157] In some aspects, the decrease in fat mass can be at least about 0.5 kg, or at least about 1.0 kg, or at least about 1.5 kg, or at least about 2.0 kg, or at least about 2.5 kg, or at least about 3.0 kg, or at least about 3.5 kg, or at least about 4.0 kg, or at least about 4.5 kg, or at least about 5.0 kg.

[00158] In some aspects, the present disclosure provides a method for increasing the concentration of L-citrulline in plasma in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing the concentration of L-citrulline in plasma in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing the concentration of L-citrulline in plasma in a subject with short bowel syndrome, wherein the

GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00159] In some aspects, the increase in concentration in L-citrulline in plasma can be at least about 5 μmol/L, or at least about 10 μmol/L, or at least about 15 μmol/L, or at least about 20 μmol/L.

[00160] In some aspects, the present disclosure provides a method for increasing urine volume output in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of increasing urine volume output in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for increasing urine volume output in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00161] In some aspects, the increase in urine volume output can be at least about 400 mL/day, or at least about 500 mL/day, or at least about 600 mL/day, or at least about 700 mL/day, or at least about 800 mL/day, or at least about 900 mL/day, or at least about 1000 mL/day.

[00162] In some aspects, the present disclosure provides a method for decreasing oral fluid intake in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of decreasing oral fluid intake in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for decreasing oral fluid intake in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00163] In some aspects, the decrease in oral fluid intake can be at least about 400 mL/day, or at least about 500 mL/day, or at least about 600 mL/day, or at least about 700 mL/day, or at least about 800 mL/day, or at least about 900 mL/day, or at least about 1000 mL/day.

[00164] In some aspects, the present disclosure provides a method for decreasing parenteral support volume in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of decreasing parenteral support volume in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for decreasing parenteral support volume in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00165] In some aspects, the decrease in parenteral support volume can be at least about 400 mL/day, or at least about 500 mL/day, or at least about 600 mL/day, or at least about 700 mL/day, or at least about 800 mL/day, or at least about 900 mL/day, or at least about 1000 mL/day.

[00166] In some aspects, the present disclosure provides a method for decreasing plasma aldosterone concentration in a subject with short bowel syndrome, the method comprising administering to the subject at least one therapeutically effective amount of a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide). The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in a method of decreasing plasma aldosterone concentration in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount. The present disclosure provides a GLP-2 analog peptide composition of the present disclosure (*e.g.*, apraglutide) for use in the manufacture of a medicament for decreasing plasma aldosterone concentration in a subject with short bowel syndrome, wherein the GLP-2 analog peptide composition of the present disclosure is for administration to the subject in at least one therapeutically effective amount.

[00167] In some aspects, the decrease in plasma aldosterone concentration can be at least about 500 pmol/L, or at least about 750 pmol/L, or at least about 1000 pmol/L, or at least about 1250

pmol/L, or at least about 1500 pmol/L, or at least about 1750 pmol/L, or at least about 2000 pmol/L, or at least about 2250 pmol/L, or at least about 2500 pmol/L, or at least about 2750 pmol/L, or at least about 3000 pmol/L.

[00168] In some aspects of the preceding methods, an increase can be an increase of at least about 5%, or at least about 10%, or at least about 15%, or at least about 20%, or at least about 25%, or at least about 30%, or at least about 35%, or at least about 40%, or at least about 45%, or at least about 50%, or at least about 55%, or at least about 60%, or at least about 65%, or at least about 70%, or at least about 75%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 99% as compared to a control level. In some aspects, the control level is the amount prior to administration of the GLP-2 analog peptide composition of the present disclosure.

[00169] In some aspects of the preceding methods, a decrease can be a decrease of at least about 5%, or at least about 10%, or at least about 15%, or at least about 20%, or at least about 25%, or at least about 30%, or at least about 35%, or at least about 40%, or at least about 45%, or at least about 50%, or at least about 55%, or at least about 60%, or at least about 65%, or at least about 70%, or at least about 75%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 99% as compared to a control level. In some aspects, the control level is the amount prior to administration of the GLP-2 analog peptide composition of the present disclosure.

[00170] In some aspects, the increase or decreases recited by the preceding methods are after at least about four weeks of treatment with the GLP-2 analog peptide composition of the present disclosure.

[00171] In some aspects, the short bowel syndrome can be short bowel syndrome intestinal insufficiency (SBS-II). In some aspects, the short bowel syndrome can be short bowel syndrome intestinal failure.

[00172] Unless otherwise stated, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

EXAMPLES

[00173] The disclosure now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present disclosure, and which are not intended to limit the disclosure.

Example 1 – Parenteral Support Volume Reduction for Short Bowel Syndrome (SBS) Patients Administered a GLP-2 Analog

[00174] This Example describes determination of parenteral support (PS) volume for SBS patients receiving the GLP-2 analog apraglutide. Subjects received 5 mg once a week subcutaneous injection of apraglutide for subject weighing 50 kg or more, and 2.5 mg for subjects with body weight lower than 50 kg. *See*, for example, **FIG. 1**, which is a flow chart of the Optimization and Stabilization periods in this Example.

[00175] In collaboration with the investigator, *i.e.*, medical professional, the subject selected an individual drinking menu which can be adjusted at any visit during the optimization phase, that was adhered to for all further fluid balance assessments (*i.e.*, only during the 48-hr balance periods) during the course of the trial. The average drinking volume was ≥1.0 L to ≤ 3.5 L/day. A deviation during the 48-hour balance periods of ±10% to the defined volume was determined acceptable.

[00176] Subjects received the subject diary, entered the screening period and the first optimization visit was scheduled between 7 days and 4 weeks from the initial Screening Visit.

Optimization Phase

[00177] The optimization phase aimed to improve the fluid balance of the subject by changing the PS volume and composition according to the institutional practice prior to treatment with apraglutide. Additionally, the optimization phase evaluated if it was safe for the subject to adhere to the proposed drinking menu, if the subject was comfortable with the drinking menu and if the subject could adhere to the protocol requirements.

[00178] The PS volume and drinking volume were adjusted throughout the optimization visits to reach the following criteria:

Average drinking volume of ≥1 L and ≤3.5 L per day and

Average urine volume of ≥ 0.8 L and ≤ 2.5 L per day.

First Optimization Visit (Visit 2a):

[00179] The subject recorded drinking volume and urinary output via the diary, for the 48-hour period prior to the first visit. In addition, the subject recorded in the diary PS volume and composition, and other PS details at the investigator's discretion. Based on clinical assessment, urinary output, PS volume and composition, drinking menu, the investigator evaluated whether the subject was considered optimized. If the subject was not considered optimized, a second optimization phase visit (Visit 2b) was scheduled. If the subject was not comfortable with the drinking menu or had difficulties with the protocol requirements, the investigator also could

schedule another optimization visit at investigator's discretion. If the subject was considered optimized at Visit 2a, he/she entered stability testing.

Second Optimization Visit (Visit 2b):
[00180] The outcome of the modified PS and/or and drinking menu must be evaluated at Visit 2b. The 48-hour fluid balance was assessed according to above criteria. If the subject was considered optimized at Visit 2b, stability testing started; if not, a third optimization visit (Visit 2c) was scheduled.

Third Optimization Visit (Visit 2c):
[00181] The outcome of the modified PS and/or drinking menu was evaluated at Visit 2c. If the subject was considered optimized at Visit 2c, stability testing started. The subject was a screening failure of the optimization phase if he/she did not meet the criteria at the third optimization visit. For medical monitor review, the eligibility form was completed, signed and submitted to the medical monitor prior to subject proceeding to stability testing. The eligibility form contained information regarding key inclusion and exclusion criteria. The medical monitor or sponsor approved prior to the subject entering stabilization testing.

Stability Testing
[00182] Stability testing was mandatory, and further optimization of PS and the drinking menu cannot occur during this period. Prior to each stability-testing visit, the subject measured his/her urine volume over 48 hours, while adhering to the pre-defined drinking menu. The subject recorded urine volume, drinking volume and PS details in the diary.
The subject fulfilled the stability criteria at either Visit 3a or 3b before they were randomized. If stability was not shown during Visits 3a or 3b due to unforeseen events (such as infections, illness or similar), a third stability-testing (Visit 3c) visit was possible at the investigator's discretion.
[00183] A subject was considered stable if at any stability testing visit, all of the following criteria were met:

- Actual PS usage (volume) matched prescribed PS (±10% deviation in volume Was acceptable)
- Average urine volume at the last optimization visit and stability testing visit matched (a maximum of ±25% deviation from last optimization visit was acceptable)
- Average drinking volume was constant (±10% deviation from daily drinking

menu defined during optimization phase was acceptable, and if between 1.0 and 3.5 L per day), and

- Average urinary volume is ≥0.8 L and ≤2.5 L per day

[00184] If the subject did not meet the criteria, he/she was considered a screen failure. For the medical monitor review, the eligibility form was completed, signed and submitted to the medical monitor after the last stabilization visit. The subject did not proceed to randomization without the approval of the medical monitor or sponsor. At the time of Visit 4, once the subject was reassessed as stable and all inclusion and exclusion criteria were re-confirmed by the investigator, the subject was then randomized.

[00185] The first treatment visit was thus Visit 4. All data collected at this visit were considered baseline values including:

Baseline PS (volume in L/week) administered in the week prior to Visit 4

Baseline daily urine (L/day) is the daily average of the 48-hour urine volume measurement prior to the baseline visit (Visit 4)

Treatment Period

[00186] Every four weeks from start of apraglutide treatment, a medical professional assessed the urinary volume reported for the 48-hour balance period by the subject.

[00187] The average daily urinary volume (*i.e.*, the volume reported for the 48 hours divided by 2) was then compared to the baseline, treatment day 0, average daily urinary volume obtained in the 48-hour balance period prior to baseline. During the 48-hour balancing period, the subject adhered to the predetermined drinking menu determined in the Optimization Period.

[00188] If the daily urinary volume was at least 10% higher than at baseline, the PS volume was reduced as follows:

a. Calculate the absolute daily urinary volume increase from baseline (in mL)

b. Multiply the increase by seven (*i.e.*, for each day of the week)

c. Result gives the PS volume reduction for the week

d. If the calculated PS volume reduction is at least as high as the average daily PS (days of PS) then, if safe for the subject, remove one day of PS, *i.e.*, the subject will have a day (more) off from PS

[00189] If the daily urinary volume was not 10% higher than at baseline, the PS was not reduced for stoma subjects.

[00190] For CIC subjects, further evaluation of medical factors was performed and an adjudication process occurred. CIC subjects then either underwent:

a. Change (reduce) PS
b. No change in PS
c. Inconclusive, Investigator decision
d. Change (increase) PS

[00191] For CIC subjects exhibiting weight gain due to edema, the volume of the PS was reduced with or without reduction of the calorie content of the PS. For CIC subject exhibiting weight gain without edema, the calorie content of the PS was reduced. For CIC subject exhibiting weight loss and dehydration, the volume of the PS was increased, with or without an increase in calorie content of the PS. For CIC subjects exhibiting weight loss without dehydration, the calorie content of the PS was increased.

[00192] The PS reduction process algorithm is depicted schematically in **FIG. 2**.

Example 2 – Parenteral Support Volume Reduction for Short Bowel Syndrome (SBS) Patients Administered a GLP-2 Analog

[00193] This Example describes determination of parenteral support (PS) volume for SBS patients receiving the GLP-2 analog apraglutide at alternate doses from those provided in Example 1. Subjects received 3.6 mg once a week subcutaneous injection of apraglutide for subject weighing 50 kg or more, and 1.5 mg for subjects with body weight lower than 50 kg. Methods were performed as described in detail in Example 1, with the modified doses.

EQUIVALENTS

[00194] The disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the disclosure described herein. Scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A glucagon-like peptide 2 (GLP-2) analog for use in a method of treating short bowel syndrome (SBS) in a subject receiving parenteral support (PS), comprising:

(1) administering the GLP-2 analog to the subject receiving an existing volume and frequency of the PS for a period of time; and

(2) modifying the volume and/or frequency of the PS, comprising:

(a) measuring a produced daily urine volume of the subject upon administering the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume, thereby determining a daily urine production change; and

(b) determining a modified volume and/or frequency of the PS, wherein:

(b_1) when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change;

(b_2) when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and

(b_3) when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then:

(b_3-i) the modified volume and frequency of the PS equals the existing volume and frequency of the PS;

(b_3-ii) the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or

(b_3-iii) the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS, optionally wherein the calorie content of the PS in steps (b_3-i), (b_3-ii) and (b_3-iii) is increased or decreased.

2. A method of treating short bowel syndrome (SBS) in a subject receiving a parenteral support (PS), comprising:

(1) administering a glucagon-like peptide 2 (GLP-2) analog to the subject receiving an existing volume and frequency of the PS for a period of time; and

(2) modifying the volume and/or frequency of the PS, comprising:

(a) measuring a produced daily urine volume of the subject upon administering the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume, thereby determining a daily urine production change; and

(b) determining a modified volume and/or frequency of the PS, wherein:

(b_1) when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change;

(b_2) when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and

(b_3) when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then:

(b_3-i) the modified volume and frequency of the PS equals the existing volume and frequency of the PS;

(b_3-ii) the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or

(b_3-iii) the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS, optionally wherein the calorie content of the PS in steps (b_3-i), (b_3-ii) and (b_3-iii) is increased or decreased.

3. A combination of a glucagon-like peptide 2 (GLP-2) analog and a parenteral support (PS) for use in a method of treating short bowel syndrome (SBS) in a subject, the method comprising:

(1) administering the PS to the subject at a first volume and a first frequency, and measuring a baseline daily urine volume of the subject prior to administering the GLP-2 analog to the subject;

(2) administering the GLP-2 analog to the subject;

(3) measuring a produced daily urine volume of the subject following administration of the GLP-2 analog, and comparing the produced daily urine volume to a baseline daily urine volume, thereby determining a daily urine production change;

(4) determining a modified volume and/or frequency of the PS, wherein:

(a) when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change;

(b) when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and

(c) when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then:

(c-i) the modified volume and frequency of the PS equals the existing volume and frequency of the PS;

(c-ii) the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or

(c-iii) the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS,

optionally wherein the calorie content of the PS in steps (c-i), (c-ii) and (c-iii) is increased or decreased; and

(5) administering the PS to the subject at the modified volume and/or frequency.

4. The GLP-2 analog for use of claim 1, the method of 2, or the combination for use of claim 3, wherein administering the GLP-2 analog results in an improved function of the small intestine of the subject.

5. The GLP-2 analog for use, the combination for use or the method of claim 4, wherein the daily urine production change is an increase of daily urine production.

6. The GLP-2 analog for use or the method of any one of claims 1-5, wherein steps (1) and (2) are repeated for one or more times.

7. The combination for use of any one of claims 1-5, wherein steps (2)-(5) are repeated for one or more times.

8. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-7, wherein the subject is a CIC subject.

9. The GLP-2 analog for use, the combination for use or the method of claim 8, wherein the modified volume and/or frequency of the PS for the CIC subject is based on a medical condition of the CIC subject.

10. The GLP-2 analog for use, the combination for use or the method of claim 9, wherein the CIC subject demonstrates fluid overload, and the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS.

11. The GLP-2 analog for use, the combination for use or the method of claim 9, wherein the CIC subject demonstrates dehydration, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

12. The GLP-2 analog for use, the combination for use or the method of claim 9, wherein the CIC subject demonstrates acute renal failure, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

13. The GLP-2 analog for use, the combination for use or the method of claim 9, wherein the CIC subject demonstrates a stable medical condition, and the modified volume and/or frequency of the PS equals the existing volume and/or frequency of the PS.

14. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-13, wherein the PS is an intravenous infusion comprising fluid and/or nutrients.

15. The GLP-2 analog for use, the combination for use or the method of claim 14, wherein the PS comprises fluid and electrolytes.

16. The GLP-2 analog for use, the combination for use or the method of claim 14 or 15, wherein the PS further comprises a parenteral nutrition (PN).

17. The GLP-2 analog for use, the combination for use or the method of claim 16, wherein the PN comprises protein, carbohydrate, fat, vitamins, and/or trace elements.

18. The GLP-2 analog for use, the combination for use or the method of claim 16 or 17, wherein the subject is a CIC patient demonstrating calorie overload, and the calorie content of the PN is decreased from baseline.

19. The GLP-2 analog for use, the combination for use or the method of claim 16 or 17, wherein the subject is a CIC patient demonstrating malnutrition and/or weight loss, and the calorie content of the PN is increased.

20. The GLP-2 analog for use, the combination for use or the method of claim 15, wherein step (2) further comprises determining the existing volume of PS per week.

21. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-20, wherein the GLP-2 analog is teduglutide, glepaglutide, apraglutide, or a pharmaceutically acceptable salt thereof.

22. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-20, wherein the GLP-2 analog is apraglutide or a pharmaceutically acceptable salt thereof.

23. The GLP-2 analog for use, the combination for use or the method of claim 22, wherein the apraglutide is a sodium salt of apraglutide.

24. The GLP-2 analog for use, the combination for use or the method of claim 22 or 23, wherein the apraglutide or pharmaceutically acceptable salt thereof is administered at a dose of:

(i) about 2.5 mg/week of apraglutide when the subject has a body weight of less than 50 kg, or

(ii) about 5 mg/week of apraglutide when the subject has a body weight greater than or equal to 50 kg.

25. The GLP-2 analog for use, the combination for use or the method of claim 22 or 23, wherein the apraglutide or pharmaceutically acceptable salt thereof is administered at a dose of:

(i) about 1.5 mg/week of apraglutide when the subject has a body weight of less than 50 kg, or

(ii) about 3.6 mg/week of apraglutide when the subject has a body weight greater than or equal to 50 kg.

26. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-25, wherein the GLP-2 analog is administered to the patient once weekly.

27. The GLP-2 analog for use, the combination for use or the method of claim 26, wherein the GLP-2 analog is apraglutide or a pharmaceutically acceptable salt thereof.

28. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-20, wherein the GLP-2 analog is administered twice weekly.

29. The GLP-2 analog for use, the combination for use or the method of claim 28, wherein the GLP-2 analog is glepaglutide or a pharmaceutically acceptable salt thereof.

30. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-20, wherein the GLP-2 analog is administered daily.

31. The GLP-2 analog for use, the combination for use or the method of claim 30, wherein the GLP-2 analog is teduglutide or a pharmaceutically acceptable salt thereof.

32. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-31, wherein the method further comprises: (3) administering the modified volume and/or frequency of the PS to the subject.

33. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-32, wherein the method further comprises measuring a baseline daily urine volume of the subject prior to administering the GLP-2 analog.

34. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-33, wherein the method further comprises determining the modified volume and/or frequency of the PS at 2, 3, 4, 5, 6 or 7 days after start of administering the GLP-2 analog.

35. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-34, wherein the method further comprises determining the modified volume and/or frequency of the PS at 1, 2, 3, 4, 5, 6, 7, 8, or more than 8 weeks after start of administering the GLP-2 analog.

36. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-33, wherein the modified volume and/or frequency of the PS is determined weekly, biweekly, triweekly, or every four weeks.

37. The GLP-2 analog for use, the combination for use or the method of claim 36, wherein the modified volume and/or frequency of the PS is determined every four weeks.

38. The GLP-2 analog for use, the combination for use or the method of any one of claims 1-37, wherein the modified volume and/or frequency of the PS reduces risk of an adverse effect from administering the GLP-2 analog.

39. The GLP-2 analog for use, the combination for use or the method of claim 38, wherein the adverse effect is fluid overload.

40. An *in vitro* method for determining a modified volume and/or frequency of parenteral support (PS) to be administered to a subject having short bowel syndrome (SBS) and who is receiving treatment with a glucagon-like peptide 2 (GLP-2) analog, comprising:

(1) measuring a baseline daily urine volume of the subject prior to administration of the GLP-2 analog, wherein the subject has received an existing volume and frequency of PS;

(2) measuring a produced daily urine volume of the subject following administration of the GLP-2 analog;

(3) comparing the produced daily urine volume to the baseline daily urine volume, thereby determining a daily urine production change; and

(4) determining a modified volume and/or frequency of the PS, wherein:

(a) when the daily urine production change is about 10% increase or higher, then the modified volume of the PS per week equals the existing volume of the PS per week minus 7 times of the daily urine production change;

(b) when the daily urine production change is less than about 10% increase and the subject is a stoma subject, then the modified volume and frequency of the PS equals the existing volume and frequency of the PS; and

(c) when the daily urine production change is less than about 10% increase and the subject is a colon-in-continuity (CIC) subject, then:

(c-i) the modified volume and frequency of the PS equals the existing volume and frequency of the PS;

(c-ii) the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS; or

(c-iii) the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS,

optionally wherein the calorie content of the PS in steps (c-i), (c-ii) and (c-iii) is increased or decreased.

41. The method of claim 40, wherein the daily urine production change is an increase of daily urine production.

42. The method of claim 40 or 41, wherein steps (1) to (4) are repeated for one or more times.

43. The method of any one of claims 40-42, wherein the subject is a CIC subject.

44. The method of claim 43, wherein the daily urine production change is less than about 10% increase and the modified volume and/or frequency of the PS for the CIC subject is based on a medical condition of the CIC subject.

45. The method of claim 44, wherein the CIC subject demonstrates fluid overload, and the modified volume and/or frequency of the PS is lower than the existing volume and/or frequency of the PS.

46. The method of claim 44, wherein the CIC subject demonstrates dehydration, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

47. The method of claim 44, wherein the CIC subject demonstrates acute renal failure, and the modified volume and/or frequency of the PS is higher than the existing volume and/or frequency of the PS.

48. The method of claim 44, wherein the CIC subject demonstrates a stable medical condition, and the modified volume and/or frequency of the PS equals the existing volume and/or frequency of the PS.

49. The method of any one of claims 40-48, wherein the PS is an intravenous infusion comprising fluid and/or nutrients.

50. The method of claim 49, wherein the PS comprises fluid and electrolytes.

51. The method of claim 49 or 50, wherein the PS further comprises a parenteral nutrition (PN).

52. The method of claim 51, wherein the PN includes protein, carbohydrate, fat, vitamins, and/or trace elements.

53. The method of claim 51 or 52, wherein the subject is a CIC patient demonstrating calorie overload, and the calorie content of the PN is decreased from baseline.

54. The method of claim 51 or 52, wherein the subject is a CIC patient demonstrating malnutrition and/or weight loss, and the calorie content of the PN is increased.

55. The method of any one of claims 40-54, wherein the GLP-2 analog is teduglutide, glepaglutide, apraglutide, elsiglutide, or a pharmaceutically acceptable salt thereof.

56. The method of claim 55, wherein the GLP-2 analog is apraglutide or a pharmaceutically acceptable salt thereof.

57. The method of claim 56, wherein the apraglutide is a sodium salt of apraglutide.

58. The method of claim 55, wherein the GLP-2 analog is glepaglutide or a pharmaceutically acceptable salt thereof.

59. The method of claim 55, wherein the GLP-2 analog is teduglutide or a pharmaceutically acceptable salt thereof.

60. The method of any one of claims 40-59, wherein the modified volume and/or frequency of the PS is determined at 2, 3, 4, 5, 6 or 7 days after start of administering the GLP-2 analog.

61. The method of any one of claims 40-60, wherein the modified volume and/or frequency of the PS is determined at 1, 2, 3, 4, 5, 6, 7, 8, or more than 8 weeks after start of administering the GLP-2 analog.

62. The method of any one of claims 40-61, wherein the modified volume and/or frequency of the PS is determined weekly, biweekly, triweekly, or every four weeks.

63. The method of claim 62, wherein the modified volume and/or frequency of the PS is determined every four weeks.