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(54) Title: GLP-2 COMPOUNDS, FORMULATIONS, AND USES THEREOF

(57) Abstract: The present invention relates to novel compositions comprising human glucagon-like peptide-2 (GLP-2) peptides, pharmaceutical compositions, and uses of these and other GLP-2 compounds, compositions and formulations, including methods of treating gastrointestinal disorders and increasing nutrient absorption therewith.

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GLP-2 COMPOUNDS, FORMULATIONS, AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to novel pharmaceutical formulations comprising GLP-2 compounds and the use of these and other GLP-2 compounds in modulating physiological responses associated with the gastrointestinal systems of mammals.

BACKGROUND OF THE INVENTION

The treatment of gastrointestinal disorders poses a continuing challenge for the medical community, particularly in children who are at risk of developing disorders such as gastroesophageal reflux disease (GERD), inflammatory bowel disease including Crohn' disease, and short bowel syndrome (SBS). Prematurely born neonates constitute a particular challenge because of the immature digestive system impeding absorption of nutrients and causing failure to thrive. The immaturity may result in necrotizing enterocolitis (NEC) that can be fatal.

Many regulatory cytokines have been identified as linked to intestinal development, including cholecystokinin, gastrin, secretin, enteroglucagon, interleukin-2 (IL-2), fibroblast growth factor (FGF), and various epidermal growth factor (EGF) protein "family" members. See, e.g., Burgess, Philos Trans R Soc Lond B Biol Sci. 1998 Jun 29;353(1370):903-9. Treatments for gastrointestinal disorders have been proposed based on the administration of growth factors such as insulin-like growth factor I (IGF-I), epidermal growth factor (EGF), and glucagon-like peptide-2 (GLP-2). For example, induction of intestinal epithelial proliferation by GLP-2 has been demonstrated (Drucker, D. J. et al (1996) Proc. Natl. Acad. Sci. USA 93: 7911-7916) and treatment of gastrointestinal diseases by cells grown in medium containing GLP-2 has been disclosed (Drucker, D.J and Keneford, J.R., WO 96/32414). International Patent Applications WO 97/31943, WO 98/08872, WO 96/32414, WO 98/03547, WO 99/43361, and WO 97/39031 disclose GLP-2 peptides including GLP-2 analogs and derivatives and make mention of the use of such peptides in the treatment of gastrointestinal disorders. International Patent Applications WO 99/43361 and WO 01/49314 disclose pharmaceutical compositions comprising GLP-2 peptides that also may be useful for such purposes.

Despite evidence that these and other growth factors may be useful in treating gastrointestinal disorders in adults, the effectiveness of treating gastrointestinal disorders in children using such growth factors remains uncertain. Primarily, this is because growth factor-based treatments that are effective in adults often fail in children. For example, in

contrast to the adult gut, the immature intestine is refractory to subcutaneously infused insulin-like growth factor I (IGF-I). See, e.g., Shoubridge et al., Am J Physiol Gastrointest Liver Physiol 281: G1378-G1384, 2001. Moreover, the effectiveness of hormones in inducing physiological effects in infants is often tied to certain stages in maturation. See, e.g., Lebenthal et al., JPEN J Parenter Enteral Nutr. 1999 Sep-Oct;23(5 Suppl):S3-6. Furthermore, significant differences in drug disposition exist between neonates, older infants, and adults, which also impact the effectiveness of various pharmaceutical treatments in children versus adults. Morselli, Clin Pharmacokinet. 1976;1(2):81-98.

There also remain shortcomings in several growth factor compositions that may limit their usefulness in both children and adults. For example, solubility limitations and the low stability against the actions of endogenous diaminopeptidyl peptidase are believed to be likely to limit the usefulness of many known GLP-2 compounds. While much attention has been focused on the pharmacological properties of GLP-2 compounds, hitherto little is known about their physico-chemical and solution structural properties. Such knowledge can be a prerequisite for rational handling during, e.g., production, purification and formulation. For example, it is an important technical challenge to ensure prolonged stability during storage (shelf life) of many protein based drug products due to the inherent lability of macromolecules. Hence, proteins are sensitive to both chemical and physical degradation unlike many small molecules. Chemical degradation involves covalent bonds, such as hydrolysis, racemization, oxidation or crosslinking. Physical degradation involves conformational changes relative to the native structure, which includes loss of higher order structure, aggregation, precipitation or adsorption to surfaces. GLP-2 is known to be prone to instability due to aggregation. Both degradation pathways may ultimately lead to loss of biological activity of the protein drug.

For these and other reasons, there remains a need for alternative methods of inducing, promoting, and/or enhancing physiological responses associated with the treatment and/or prevention of gastrointestinal disorders in children and adults, but especially in infants, as well as (in the context of such treatment and/or prevention methods and independently for other uses) new GLP-2 compounds and compositions. The invention described herein provides such methods and novel compositions. These and other advantages of the invention, as well as additional inventive aspects and features, will be apparent from the description of the invention provided herein.

SUMMARY OF THE INVENTION

The invention described herein provides novel pharmaceutical formulations of GLP-2 compounds and uses thereof.

In a first exemplary aspect, the invention provides a method for inducing, enhancing, and/or promoting one or more physiological responses associated with the treatment and/or prevention of a disorder, disease, or condition that is associated with the inability or failure to absorb a desired amount of nutrients from the intestine, comprising administering to the infant a composition comprising an amount of a GLP-2 compound sufficient to provide an increase in absorption of nutrients from the intestine. The GLP-2 compound composition typically and desirably also comprises one or more pharmaceutically acceptable vehicles, diluents, excipients, carriers, protectants, flavorants, preservatives, stabilizers, activity enhancers, buffers, colorants, wetting agents, lubricants, tabletting agents, solvents, solutes, anti-oxidants, biostatic agents, suspending agents, isotonic agents, thickening agents, adjuvants, emulsifiers, salts, aromatic agents, solubilizers, or any combination thereof. In specific exemplary aspects, the infant is a premature human infant diagnosed as suffering from a disease, disorder, or condition associated with poor absorption from the intestine. In these and other specific exemplary aspects, the GLP-2 compound in the composition is in a concentration of about 0.001-0.5 mg/ml.

In another exemplary aspect, the invention provides a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound in a concentration of about 0.001-0.5 mg/ml in a volume sufficient to provide a detectable increase in absorption of nutrients from the intestine.

In another exemplary aspect, the invention provides a composition comprising a GLP-2 compound in a concentration from about 0.001-0.1 mg/ml in a volume sufficient to detectably increase absorption of nutrients from the intestine of a premature human infant having an impaired ability to absorb nutrients from the intestine and a pharmaceutically acceptable carrier.

In another exemplary aspect, the invention provides a pharmaceutical composition comprising a GLP-2 compound in a concentration of about 0.001 mg/ml-0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a target population of premature human infants afflicted with a condition associated with the inability to absorb sufficient amount of nutrients from the intestine. Such compositions

optionally can include one more pharmaceutically acceptable carriers, diluents, and the like, as described above.

In another exemplary aspect, the invention provides a kit for preparing a pharmaceutically acceptable composition for promoting the absorption of nutrients from the intestine comprising:

a first component comprising a predetermined lyophilized amount of a GLP-2 compound;

a second component different from the first component comprising a predetermined volume of a pharmaceutically acceptable aqueous solution; whereby mixture of the first and second components results in a liquid pharmaceutically acceptable composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml and in a volume sufficient to increase the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 The amino acid sequence of the 33 residues human GLP-2. The N-terminal His-Ala indicates the sequence cleaved of aminopeptidase dipeptidyl peptidase IV during metabolism of GLP-2. The Arg20 and Lys30 residues are the two basic amino acid residues in GLP-2.

Fig. 2 Tissue-specific processing of proglugacon in pancreas and intestine.

Fig. 3 Sequence alignment of the highly conserved GLP-2 peptide. Amino acid residues in bold represent those that differ from the human GLP-2 sequence.

Fig. 4 Quantification of GLP-2R RNA distribution in various rat tissue.

Fig. 5 L17K/K30R-GLP-2 (1-33) acylated with β-alanine C16.

Fig. 6 Examples with chemical structure of the use of different spacers according to the invention with the lipophilic substituent being a hexadecanoyl.

Fig. 7 S.cerevisiae plasmid for the expression and secretion of GLP-2 peptide analogs.

Fig. 8. SEQ ID NO. 1, SEQ ID NO. 2, and SEQ ID NO. 3.

DETAILED DESCRIPTION OF THE INVENTION

The invention described herein provides novel pharmaceutical formulations of GLP-2 compounds and novel methods of using these novel formulations and other GLP-2 compounds and/or GLP-2 compound formulations in the induction, promotion, and/or enhancement of physiological responses, primarily responses associated with the gastrointestinal systems of mammals (e.g., a human patient). In specific aspects of the invention, these methods can be used to promote, induce, and/or enhance the treatment and/or prevention of gastrointestinal diseases, disorders, or conditions. In a specific aspect, the invention provides new methods of inducing, promoting, and/or enhancing such responses in children (e.g., infants such as, for example, neonates and prematurely-born human infants).

In one particular aspect, the invention relates to (i.e., provides) a method for the treatment of a premature human infant unable to absorb sufficient amount of nutrients from the intestine comprising administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration of less than about 0.5 mg/ml (e.g., about 0.005-0.5 mg/ml, about 0.01-0.5 mg/ml, about 0.05-0.5 mg/ml, about 0.1-0.5 mg/ml, about 0.001-0.1 mg/ml, about 0.001-0.05 mg/ml, about 0.001-0.01 mg/ml, about 0.01-0.5 mg/ml, or about 0.01-0.1 mg/ml) in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant.

In another particular aspect, the invention relates to pharmaceutical composition (i.e., a composition that detectably induces, promotes, and/or enhances a pharmacological effect in a mammal and preferably that is considered pharmaceutically acceptable for administration to a human) comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration of less than about 0.5 mg/ml (e.g., about 0.001-0.05 mg/ml, about 0.001-0.01 mg/ml, about 0.05-0.01 mg/ml, about 0.05-0.1 mg/ml, etc.) in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients from the intestine and optionally, a pharmaceutically acceptable carrier, diluent, vehicle, preservative, stabilizer, activity-enhancing agent, or the like, or a combination thereof.

In another aspect, the invention relates to a kit for use in the treatment of a premature human infant unable to absorb sufficient amount of nutrients from the intestine comprising a first component comprising a predetermined lyophilized amount of a GLP-2

compound and a second component different from the first component comprising a predetermined volume of aqueous solution, whereby mixture of the first and second components results in a liquid composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration of less than about 0.5 mg/ml (more particular examples of which are recited elsewhere herein with reference to this and other aspects) in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant.

The term "premature human infant" means any infant born prior to about 37 weeks of gestation. The term includes both healthy infants and infants with a damaged and/or immature intestine. The treatment and/or prevention of disorders, diseases, and conditions is a preferred aspect of the invention; however, the induction, promotion, and/or enhancement of physiological responses associated with the treatment and/or prevention of gastrointestinal diseases, disorders, and conditions in non-premature human infants, children, and (at least in certain contexts) even adults also are important aspects of the invention.

The bowels of the infant born at term are prepared for immediate digestion of food; however this is not the case for a premature baby. Therefore, the discovery that GLP-2 compounds can promote the maturation of the intestines of premature human infants (e.g., premature neonates) to accelerate and improve oral feeding and/or promote the healing of damaged tissue is an advantageous aspect of the invention.

As used herein, the term "GLP-2 compound" means any GLP-2 receptor agonist. The term encompasses GLP-2 peptides, and analogues thereof, as well as GLP-2 derivatives.

A GLP-2 receptor agonist typically binds to a GLP-2 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below about 1 μM, e.g. about 1 nM-750 nM, such as about 500 nM or less, about 250 nM or less, about 100 nM or less, about 75 nM or less, or about 50 nM or less. Examples of suitable GLP-2 compounds that can be useful in practicing many of the methods of the invention are disclosed in e.g. WO 96/29342, WO 97/31943, WO 98/08872, WO 98/03547, WO 96/32414, WO 97/39031, international patent application with application number DK03/00694, and Danish patent application PA 2003 00451, the content of which are incorporated herein by reference in their entirety. In certain aspects, the GLP-2 compound is an intestinotrophic molecule, such as an intestinotrophic GLP-2 peptide.

The term "GLP-2 peptide" as used herein means any biologically active protein, polypeptide, or peptide (which terms are generally used interchangeably throughout unless otherwise stated or clearly contradicted by context) comprising the amino acid sequence 1-

33 of native human GLP-2 (SEQ ID NO:1) or a sequence having at least about 65%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or more (e.g., about 70-99%) amino acid sequence identity to this sequence. Thus, "GLP-2 peptides" include, but is not limited to, native human GLP-2 and analogs thereof. A GLP-2 peptide can have any suitable amino acid sequence or other features, so long as the peptide at least substantially retains (e.g., retains at least about 50%, at least about 75%, at least about 90%, about 100% or more, about 125% or more, about 150% or more, about 200% or more, etc.) of the ability to induce, promote, and/or enhance at least one physiological response associated with the administration of GLP-2 (e.g., the ability to detectably promote the growth of gastrointestinal tissue in a mammalian host over a period of time, the ability to detectably inhibit apoptosis of certain cells (as compared to the individual or a population of substantially similar individuals), the ability to detectably reduce intestinal permeability, the ability to detectably stimulate enterocyte glucose transport, the ability to detectably increase adenylate cyclase activity, and/or the ability to detectably inhibit gastric emptying and gastric acid secretion).

Human GLP-2 is a 33 amino acid residue peptide produced in intestinal L-cells and released following nutrient intake. The amino acid sequence of human GLP-2 is set forth in Fig. 1.

The term "GLP-2" as used herein refers to a protein comprising amino acids 1-33 of native human GLP-2 (SEQ ID NO:1) and proteins with a slightly modified amino acid sequence, for instance, proteins comprising a modified N-terminal end including N-terminal amino acid deletions or additions (so long as those proteins substantially retain the activity of GLP-2). "GLP-2" within the above definition also includes natural allelic variations that may exist and occur from one individual to another. Also, degree and location of glycosylation or other post-translation modifications may vary depending on the chosen host cells and the nature of the host cellular environment in which the GLP-2 is produced.

The terms “analog” or “analogs”, as used herein, designate a GLP-2 peptide having the sequence similar to SEQ ID NO:1, but wherein one or more amino acids of SEQ ID NO:1 ("the parent sequence") have been substituted, deleted, and/or inserted and/or where one or more amino acid residues have been added to the N and/or C terminus of SEQ ID NO:1. The “analog” or “analogs” within this definition still have GLP-2 activity, desirably as measured by the ability to exert a trophic effect on the small or large intestine (although other suitable markers of GLP-2 activity also or alternatively can be used in other aspects). In one aspect an analog is about 70 % identical with the sequence of SEQ ID NO:1. In another aspect an analog is about 80 % identical with the sequence of SEQ ID NO:1. In yet another aspect an

analog is about 90 % identical with the sequence of SEQ ID NO:1. In a further aspect an analog is 95 % identical with the sequence of SEQ ID NO:1.

In another aspect an analog is a GLP-2 peptide, wherein a total of up to ten amino acid residues of SEQ ID NO:1 have been exchanged with any amino acid residue. In a further aspect an analog is a GLP-2 peptide, wherein a total of up to five amino acid residues of SEQ ID NO:1 have been exchanged with any amino acid residue. In a further aspect an analog is a GLP-2 peptide, wherein a total of up to three amino acid residues of SEQ ID NO:1 have been exchanged with any amino acid residue. In a further aspect an analog is a GLP-2 peptide, wherein a total of up to two amino acid residues of SEQ ID NO:1 have been exchanged with any amino acid residue. In a further aspect an analog is a GLP-2 peptide, wherein a total of one amino acid residue of SEQ ID NO:1 have been exchanged with any amino acid residue. Thus, for example, in one aspect of the invention the GLP-2 compound is a GLP-2 peptide, wherein a total of up to 5 amino acid residues have been exchanged with any α-amino acid residue, such as 4 amino acid residues, 3 amino acid residues, 2 amino acid residues, or 1 amino acid residue.

In one aspects, the GLP-2 peptide used in the methods of the invention and/or included in the formulation of the invention, is a GLP-2 peptide with a half-life lower than about 2 hours. The "half-life" as used herein means the half-life of detectable functional GLP-2 compound in adult human plasma. The actual half-life in a premature human infant may vary considerably dependent on the maturity in the infant of clearance systems, e.g. renal and/hepatic clearance systems. A GLP-2 peptide with a half-life lower than about 2 hours according to the above definition includes wild type human GLP-2(1-33). In one embodiment the GLP-2 compound has a half-life lower than about 1 hour, such as lower than about 30 min, such as lower than about 20 min, such as lower than 10 min.

In particular aspects, the GLP-2 peptide used in the methods of the invention and/or included in the formulation of the invention comprises, consists, or consists essentially of an amino acid sequence according to the formula:

His-X^2-X^3-Gly-X^5-Phe-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-X^{18}-Ala-X^{20}-X^{21}-Phe-Ile-X^{24}-Trp-Leu-Ile-X^{28}-Thr-Arg-Ile-Thr-X^{33}-X^{34} (formula I)

or a fragment thereof, wherein "X" represents any suitable amino acid residue. In more particular aspects, X^2 is Ala, Val or Gly; X^3 is Asp, or Glu; X^5 is Ser, or Lys; X^7 is Ser, or Lys; X^8 is Asp, Glu, or Lys; X^9 is Asp, Glu, or Lys; X^{10} is Met, Lys, Leu, Ile, or Nor-Leucine; X^{11} is Asn, or Lys; X^{12} is Thr, or Lys; X^{13} is Ile, or Lys; X^{14} is Leu, or Lys; X^{15} is Asp, or Lys; X^{16} is

Asn, or Lys; X^{17} is Leu, or Lys; X^{18} is Ala, or Lys; X^{20} is Arg, or Lys; X^{21} is Asp, or Lys; X^{24} is Asn, or Lys; X^{28} is Gln, or Lys; and/or X^{33} is Asp, Glu, or Lys, X^{34} is OH, Lys, Arg, Arg-Lys, Lys-Arg, Arg-Arg, or Lys-Lys.

In other particular aspects, the GLP-2 peptide used in the methods and/or included in the formulations of the invention comprises (includes), consists, or consists essentially of an amino acid sequence according to the formula:

His-X^2-X^3-Gly-X^5-Phe-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-X^{18}-Ala-X^{20}-X^{21}-Phe-Ile-X^{24}-Trp-Leu-Ile-X^{28}-Thr-X^{30}-Ile-Thr-X^{33}-X^{34} (formula II)

or a fragment thereof; wherein "X" represents any suitable amino acid residue. In particular aspects, X^2 is Ala, Val or Gly; X^3 is Asp, or Glu; X^5 is Ser, or Lys; X^7 is Ser, or Lys; X^8 is Asp, Glu, or Lys; X^9 is Asp, Glu, or Lys; X^{10} is Met, Lys, Leu, Ile, or Nor-Leucine; X^{11} is Asn, or Lys; X^{12} is Thr, or Lys; X^{13} is Ile, or Lys; X^{14} is Leu, or Lys; X^{15} is Asp, or Lys; X^{16} is Asn, or Lys; X^{17} is Leu, or Lys; X^{18} is Ala, or Lys; X^{20} is Arg, or Lys; X^{21} is Asp, or Lys; X^{24} is Asn, or Lys; X^{28} is Gln, or Lys; X^{30} is Arg, or Lys; X^{33} is Asp, Glu, or Lys, and/or X^{34} is OH, Lys, Arg, Arg-Lys, Lys-Arg, Arg-Arg, or Lys-Lys.

With reference to either formula I or formula II, GLP-2 peptides useful in specific method and/or formulation of aspects of the invention can be characterized as follows. In one aspect X^2 is Ala. In one aspect X^2 is Gly. In one aspect X^3 is Asp. In one aspect X^3 is Glu. In one aspect X^5 is Ser. In one aspect X^7 is Ser. In one aspect X^8 is Asp. In one aspect X^8 is Glu. In one aspect X^9 is Asp. In one aspect X^9 is Glu. In one aspect X^{10} is selected from the group consisting of Met, Leu, Ile, and Nor-Leucine. In one aspect X^{11} is Asn. In one aspect X^{12} is Thr. In one aspect X^{13} is Ile. In one aspect X^{14} is Leu. In one aspect X^{15} is Asp. In one aspect X^{16} is Asn. In one aspect X^{17} is Leu. In one aspect X^{18} is Ala. In one aspect X^{21} is Asp. In one aspect X^{24} is Asn. In one aspect X^{28} is Gln. In one aspect X^{33} is Asp. In one aspect X^{33} is Glu. GLP-2 peptides suitable for use in methods and/or formulations of the invention can be characterized by any suitable combination of such specific attributes.

In certain aspects, GLP-2 peptides used in the methods and/or formulations of the invention (and comprising, consisting, or consisting essentially of an amino acid sequence according to either formula I or formula II) can be characterized on the basis that at least one amino acid independently selected from the list consisting of X^5, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, X^{16}, X^{17}, X^{18}, X^{20}, X^{21}, X^{24}, X^{28}, and X^{33} is a Lys. In one aspect the amino acid independently selected from the list consisting of X^5, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, X^{16}, X^{17}, X^{18}, X^{20}, X^{21}, X^{24}, X^{28}, and X^{33} is Lys. In one aspect the amino acid X^5 is Lys. In one

aspect the amino acid X^7 is Lys. In one aspect the amino acid X^8 is Lys. In one aspect the amino acid X^9 is Lys. In one aspect the amino acid X^{10} is Lys. In one aspect the amino acid X^{11} is Lys. In one aspect the amino acid X^{12} is Lys. In one aspect the amino acid X^{13} is Lys. In one aspect the amino acid X^{14} is Lys. In one aspect the amino acid X^{15} is Lys. In one aspect the amino acid X^{16} is Lys. In one aspect the amino acid X^{17} is Lys. In one aspect the amino acid X^{18} is Lys. In one aspect the amino acid X^{20} is Lys. In one aspect the amino acid X^{21} is Lys. In one aspect the amino acid X^{24} is Lys. In one aspect the amino acid X^{28} is Lys. In one aspect the amino acid X^{30} is Lys. In one aspect the amino acid X^{30} is Arg. In one aspect the amino acid X^{33} is Lys. In one aspect the amino acid X^{33} is Lys. In one aspect the amino acid X^{34} is Lys. In one aspect the amino acid X^{34} is Arg. As with other characterizations of the variable amino acid residues in formula I and formula II provided herein, such GLP-2 peptides also or alternatively can be characterized by any suitable combination of these characteristics.

The phrase "a fragment thereof", as used herein, means any fragment (i.e., portion) of the referenced peptide or amino acid sequence (e.g., a fragment can refer to a portion of a formula I or formula II sequence) that is at least about 15 amino acids in length and exhibits (or at least substantially retains) some GLP-2 biological activity in a mammalian host. GLP-2 activity may be measured be GLP-2 receptor binding affinity or by any of the other measures of GLP-2 activity described herein (e.g., the detectable promotion of tissue growth in the small intestine). In one aspect the fragment comprises at least about 20 amino acids of the "parent" peptide or sequence (e.g., about 20-30 amino acids of native GLP-2). In another aspect, the fragment comprises at least about 25 amino acids of the parent. In one aspect the fragment comprises at least about 30 amino acids of the parent. The term "fragment" is used for convenience and is not meant to impart or imply any limitation on how such peptides are made or limit any other characteristics of such peptides (thus, for example, a peptide comprising a "fragment" of formula I, may actually comprise an amino acid sequence larger than formula I, for example in the context of a fusion protein comprising the "fragment" sequence).

In one aspect, the invention provides methods of using peptides comprising or consisting of a fragment and formulations that relate to peptides comprising or consisting of a fragment, wherein the fragment corresponds to formula I or formula II except for one amino acid deletion in the C-terminus, two amino acid deletions in the C-terminus, three amino acid deletions in the C-terminus, or four amino acid deletions in the C-terminus. In another aspect the fragment also or alternatively varies from formula I or formula II by one amino acid

deletion in the N-terminus, two amino acid deletions in the N-terminus, three amino acid deletions in the N-terminus, or four amino acid deletions in the N-terminus.

The term "derivative" is used in the present text to designate a peptide in which one or more of the amino acid residues have been chemically modified, *e.g.* by alkylation, acylation, ester formation, or amide formation. The term "a GLP-2 derivative" is used in the present text to designate a derivative of a GLP-2 peptide. In one aspect the GLP-2 derivative according to the present invention has GLP-2 activity as measured by, for example, the ability to bind a GLP-2 receptor (GLP-2R) and/or exert trophic effects on the small intestine or large intestine. In one aspect the GLP-2 receptor used to measure GLP-2 activity is selected from the list consisting of rat GLP-2R, mouse GLP-2R, and human GLP-2R.

The term "lipophilic substituent" refers to a lipophilic group or moiety comprising about 4-40 carbon atoms and having a solubility in water at about 20°C in the range from about 0.1 mg/100 ml water to about 250 mg/100 ml water, such as in the range from about 0.3 mg/100 ml water to about 75 mg/100 ml water. For instance, octanoic acid (C8) has a solubility in water at 20°C of 68 mg/100 ml, decanoic acid (C10) has a solubility in water at 20°C of 15 mg/100 ml, and octadecanoic acid (C18) has a solubility in water at 20°C of 0.3 mg/100 ml.

A simple system is used in the following to describe peptides, fragments, analogs, and derivatives of GLP-2 herein which will be readily apparent to the ordinarily skilled artisan. By way of illustration, R20K-GLP-2(1-31) designates a fragment of GLP-2 formally wherein the amino acid residues at positions 32 and 33 of SEQ ID NO:1 are deleted ("1-31") and the naturally occurring amino acid residue arginine at position 20 of SEQ ID NO:1 is substituted by a lysine ("R20K"). Similarly, R20K(N^{ε}-tetradecanoyl)/K30R-GLP-2(1-33) designates a derivative of a GLP-2 peptide analog formally derived from GLP-2 by exchange of the naturally occurring amino acid residue lysine in position 30 of SEQ ID NO:1 with an arginine residue and exchange of the naturally occurring amino acid residue arginine in position 20 of SEQ ID NO:1 with a lysine residue and tetradecanoylation of the ε-amino group of the lysine residue in position 20 relative to the amino acid sequence of SEQ ID NO:1. Similarly, L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33) designates a derivative of a GLP-2 peptide analog formally derived from GLP-2 by exchange of the naturally occurring amino acid residue lysine in position 30 of SEQ ID NO:1 with an arginine residue and exchange of the naturally occurring amino acid residue leucine in position 17 of SEQ ID NO:1 with a lysine residue and hexadecanoylation of the ε-amino group of the lysine residue in position 17 relative to the amino acid sequence of SEQ ID NO:1 by means of the spacer β-alanine (see, e.g., figs. 5 and 6).

The term "treatment" is meant to include both the prevention and minimization of the referenced disease, disorder, or condition (i.e., "treatment" refers to both prophylactic and therapeutic administration of a GLP-2 compound/composition unless otherwise indicated or clearly contradicted by context; however, therapeutic administration of GLP-2 compounds/compositions and prophylactic administration of GLP-2 compounds/compositions can separately be considered unique aspects of the invention). For example, in one aspect the invention provides a method of treating a condition resulting in the prevention of an expected intestinal failure or other condition leading to malabsorption of nutrients in the intestine and/or the minimization of an effect that, without treatment, would lead to malabsorption of nutrients in the intestine.

To obtain a protracted profile of action, a lipophilic substituent can be attached to the GLP-2 peptide to obtain a lipophilic GLP-2 derivative (such a lipophilic substituent can, for example, comprise about 4-40 carbon atoms, such as about 8-25 carbon atoms or about 10-20 carbon atoms, although other suitable sizes also can be used). In one aspect of the invention the lipophilic substituent comprises about 8 to about 40 carbon atoms; in another aspect about 10 to about 24 carbon atoms; in yet another aspect about 12 to about 24 carbon atoms; in yet another aspect 12 to 20 carbon atoms; in still another aspect about 12 to about 18 carbon atoms; and in yet a further aspect about 14 to about 18 carbon atoms. The size and character of a specific lipophilic substituent can impart advantageous properties to the GLP-2 peptide and accordingly can be considered a unique feature of such peptides.

The lipophilic substituent may be attached to any suitable amino group of the GLP-2 moiety or sequence by any suitable means, typically by way of a carboxyl group of the lipophilic substituent which forms an amide bond with an amino group of the amino acid residue to which it is attached. As an alternative, the lipophilic substituent may be attached to an amino acid in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid. As a further option, the lipophillic substituent may be linked to the GLP-2 moiety via an ester bond. Formally, the ester can be formed either by reaction between a carboxyl group of the GLP-2 moiety and a hydroxyl group of the substituent-to-be or by reaction between a hydroxyl group of the GLP-2 moiety and a carboxyl group of the substituent-to-be. As a further alternative, the lipophilic substituent can be an alkyl group which is introduced into a primary amino group of the GLP-2 moiety. In certain aspects of the invention a lipophilic substituent is attached to a Lys residue of the GLP-2 sequence.

In certain aspects, the GLP-2 compound is at least substantially isolated and in others the GLP-2 compound can be considered "isolated." The term "isolated GLP-2 compound"

refers to a GLP-2 compound that is at least about 50%, typically at least about 65%, and more typically at least about 75% or more free of undesirable molecules (typically such undesirable molecules are biomolecules such as nonassociated polynucleotides, lipids, carbohydrates or other materials (i.e., contaminants) that the GLP-2 compound is naturally associated with). Purity can be measured by any suitable technique including, e.g., electrophoretic analysis, antibody-based analytical techniques, mass spectrometry, differential (e.g., affinity or mass based) centrifugation, and the like. In one aspect the GLP-2 compound is an isolated GLP-2 peptide; in another aspect the GLP-2 compound is an isolated GLP-2 derivative; in yet other aspects the isolated GLP-2 compound is an isolated nonpeptide GLP-2 compound (e.g., a "small molecule" GLP-2 receptor agonist, a nucleic acid encoding a GLP-2 antibody, GLP-2 receptor antibody, or other GLP-2 peptide agonist, or an antisense or interfering nucleic acid molecule (e.g., a GLP-2 expression modulating siRNA molecule). Preferably, the isolated compound or polypeptide is substantially free from any other contaminating polypeptides or other contaminants that are found in its natural environment which would interfere with its therapeutic, diagnostic, prophylactic or research use. Preferably, the isolated compound or polypeptide has been separated from at least about 80%, such as at least about 90%, at least about 95%, or more (desirably detectably free from all) free and undesired polynucleotides, lipids, carbohydrates or other materials (i.e., contaminants).

In specific aspects of the invention the GLP-2 compound is selected from a GLP-2 compound as disclosed in any of International Patent Applications WO 97/31943, WO 98/08872, WO 96/32414, WO 98/03547, WO 99/43361, and WO 97/39031.

In specific aspects of the invention the GLP-2 compound is selected from GLP-2(1-33), 34R-GLP-2(1-34), A2G-GLP-2(1-33), A2G/34R-GLP-2(1-34), K30R-GLP-2(1-33); S5K-GLP-2(1-33); S7K-GLP-2(1-33); D8K-GLP-2(1-33); E9K-GLP-2(1-33); M10K-GLP-2(1-33); N11K-GLP-2(1-33); T12K-GLP-2(1-33); I13K-GLP-2(1-33); L14K-GLP-2(1-33); D15K-GLP-2(1-33); N16K-GLP-2(1-33); L17K-GLP-2(1-33); A18K-GLP-2(1-33); D21K-GLP-2(1-33); N24K-GLP-2(1-33); Q28K-GLP-2(1-33); S5K/K30R-GLP-2(1-33); S7K/K30R-GLP-2(1-33); D8K/K30R-GLP-2(1-33); E9K/K30R-GLP-2(1-33); M10K/K30R-GLP-2(1-33); N11K/K30R-GLP-2(1-33); T12K/K30R-GLP-2(1-33); I13K/K30R-GLP-2(1-33); L14K/K30R-GLP-2(1-33); D15K/K30R-GLP-2(1-33); N16K/K30R-GLP-2(1-33); L17K/K30R-GLP-2(1-33); A18K/K30R-GLP-2(1-33); D21K/K30R-GLP-2(1-33); N24K/K30R-GLP-2(1-33); Q28K/K30R-GLP-2(1-33); K30R/D33K-GLP-2(1-33); D3E/K30R/D33E-GLP-2(1-33); D3E/S5K/K30R/D33E-GLP-2(1-33); D3E/S7K/K30R/D33E-GLP-2(1-33); D3E/D8K/K30R/D33E-GLP-2(1-33); D3E/E9K/K30R/D33E-GLP-2(1-33); D3E/M10K/K30R/D33E-GLP-2(1-33);

D3E/N11K/K30R/D33E-GLP-2(1-33); D3E/T12K/K30R/D33E-GLP-2(1-33); D3E/I13K/K30R/D33E-GLP-2(1-33); D3E/L14K/K30R/D33E-GLP-2(1-33); D3E/D15K/K30R/D33E-GLP-2(1-33); D3E/N16K/K30R/D33E-GLP-2(1-33); D3E/L17K/K30R/D33E-GLP-2(1-33); D3E/A18K/K30R/D33E-GLP-2(1-33); D3E/D21K/K30R/D33E-GLP-2(1-33); D3E/N24K/K30R/D33E-GLP-2(1-33); D3E/Q28K/K30R/D33E-GLP-2(1-33); and combinations of any thereof.

As mentioned elsewhere herein, the GLP-2 compound in certain aspects can advantageously be a GLP-2 derivative. Any suitable GLP-2 derivative can be used in the methods and/or act as an active ingredient in the formulations of the invention. In a particular aspect, the GLP-2 derivative comprises a GLP-2 peptide (i.e., comprises a GLP-2-like amino acid sequence) according to formula II or a fragment thereof. In specific aspects, the GLP-2 derivative comprises a formula II amino acid sequence or formula II amino acid sequence fragment characterized by one or more of the following: X^2 is Ala, Val or Gly; X^3 is Asp, or Glu; X^5 is Ser, or Lys; X^7 is Ser, or Lys; X^8 is Asp, Glu, or Lys; X^9 is Asp, Glu, or Lys; X^{10} is Met, Lys, Leu, Ile, or Nor-Leucine; X^{11} is Asn, or Lys; X^{12} is Thr, or Lys; X^{13} is Ile, or Lys; X^{14} is Leu, or Lys; X^{15} is Asp, or Lys; X^{16} is Asn, or Lys; X^{17} is Leu, or Lys; X^{18} is Ala, or Lys; X^{20} is Arg, or Lys; X^{21} is Asp, or Lys; X^{24} is Asn, or Lys; X^{28} is Gln, or Lys; X^{30} is Arg, or Lys; X^{33} is Asp, Glu, or Lys; and X^{34} is OH, Lys, Arg, Arg-Lys, Lys-Arg, Arg-Arg, or Lys-Lys

In one aspect of the invention the GLP-2 compound is a GLP-2 derivative comprising a GLP-2 peptide, wherein a lipophilic substituent is attached to one or more amino acid residues at a position relative to the amino acid sequence of SEQ ID NO:1 selected from the list consisting of S5, S7, D8, E9, M10, N11, T12, I13, L14, D15, N16, L17, A18, D21, N24, and Q28. In one aspect, a lipophilic substituent is attached to an amino acid residues at the position S5 relative to the amino acid sequence of SEQ ID NO:1. In another aspect, a lipophilic substituent is attached to an amino acid residues at the position S7 relative to the amino acid sequence of SEQ ID NO:1. In one aspect, a lipophilic substituent is attached to an amino acid residues at the position D8 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position E9 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position M10 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position N11 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position T12 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position I13 relative to the amino acid

sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position L14 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position D15 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position N16 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position L17 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position A18 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position D21 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position N24 relative to the amino acid sequence of SEQ ID NO:1. In one aspect a lipophilic substituent is attached to an amino acid residues at the position Q28 relative to the amino acid sequence of SEQ ID NO:1. It is to be understood that an amino acid residues at the position relative to the amino acid sequence of SEQ ID NO:1 may be any amino acid residue and not only the amino acid residue naturally present at that position. In one aspect the lipophilic substituent is attached to a lysine. GLP-2 derivatives can be characterized by any combination of these features.

In a further aspect, the lipophilic substituent may be attached to the GLP-2 peptide by means of a spacer in such a way that a carboxyl group of the spacer forms an amide bond with an amino group of the GLP-2 peptide. A spacer typically contains at least two functional groups, one to attach to a functional group of the lipophilic substituent and the other to a functional group of the parent GLP-2 peptide. The term "spacer" is used in the present text to designate a bivalent moiety which contain at least two functional groups, one to attach to a functional group of the lipophilic substituent and the other to a functional group of the GLP-2 compound.

Examples of suitable spacers include succinic acid, lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gamma-aminobutanoyl, and dipeptide spacers (such as Gly-Lys), each of which constitutes an individual aspect of the invention. Thus, a spacer can be one of these recited amino acid residues or another suitable amino acid. In a further aspect of the invention, the spacer is an amino acid residue (typically a naturally occurring amino acid residue) except Cys or Met. In another aspect, the spacer is a dipeptide such as Gly-Lys. In a further aspect the spacer is selected from lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gamma-aminobutanoyl, each of which constitutes an individual aspect. Typically used spacers are glutamyl, aminobutyroyl, and beta-alanyl (beta-Ala). When the spacer is succinic acid, one carboxyl group thereof may form an amide bond with an amino group of the amino acid residue,

and the other carboxyl group thereof may form an amide bond with an amino group of the lipophilic substituent. When the spacer is lysyl, glutamyl, asparagyl, glycyl, beta-alanyl or gamma-aminobutanoyl, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ε-amino group of Lys and the lipophilic substituent. In one preferred aspect, such a further spacer is succinic acid which forms an amide bond with the ε-amino group of Lys and with an amino group present in the lipophilic substituent. In another preferred aspect such a further spacer is Glu or Asp which forms an amide bond with the ε-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent, that is, the lipophilic substituent is a N^{ε}-acylated lysine residue. In an aspect, the spacer is an amino acid residue except Cys or Met, or a dipeptide such as Gly-Lys. For purposes of the present invention, the phrase "a dipeptide such as Gly-Lys" means any combination of two amino acids except Cys or Met, typically a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, typically Lys, and the N-terminal amino acid residue is Ala, Arg, Asp, Asn, Gly, Glu, Gln, Ile, Leu, Val, Phe, Pro, Ser, Tyr, Thr, Lys, His or Trp. Typically, an amino group of the GLP-2 compound forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

In another aspect, the spacer is an unbranched alkane α,ω-dicarboxylic acid group comprising from about 1 to 7 methylene groups (e.g., 1-5 methylene groups, 2-4 methylene groups, 2 or 3 methylene groups, etc.), which spacer typically forms a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent. Typically, the spacer is succinic acid.

The lipophilic substituent(s) typically contain a functional group which can be attached to one of the following functional groups of an amino acid of the parent GLP-2 peptide: (a) the amino group attached to the alpha-carbon of the N-terminal amino acid, (b) the carboxy group attached to the alpha-carbon of the C-terminal amino acid, (c) the epsilon-amino group of any Lys residue, (d) the carboxy group of the R group of any Asp and Glu residue, (e) the hydroxy group of the R group of any Tyr, Ser and Thr residue, (f) the amino group of the R group of any Trp, Asn, Gln, Arg, and His residue, or (g) the thiol group of the R group of any Cys residue.

In a further aspects of the invention, a lipophilic substituent is attached to the carboxy group of the R group of any Asp and Glu residue; a lipophilic substituent is attached to the

carboxy group attached to the alpha-carbon of the C-terminal amino acid; or a lipophilic substituent is attached to the epsilon-amino group of any Lys residue.

In one aspect of the invention the spacer is an amino acid residue except a Cys residue, or a dipeptide. Examples of suitable spacers include (among others described elsewhere herein) β-alanine, gamma-aminobutyric acid (GABA), γ-glutamic acid, succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ε-amino group of Lys and the lipophilic substituent. In one aspect, such a further spacer is succinic acid which forms an amide bond with the ε-amino group of Lys and with an amino group present in the lipophilic substituent. In another aspect such a further spacer is Glu or Asp which forms an amide bond with the ε-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent, that is, the lipophilic substituent is a N^{ε}-acylated lysine residue.

In one aspect of the invention the spacer is selected from β-alanine, gamma-aminobutyric acid (GABA), γ-glutamic acid, Lys, Asp, Glu, a dipeptide containing Asp, a dipeptide containing Glu, or a dipeptide containing Lys. These and other specific spacers described herein can impart unique characteristics. As such, GLP-2 peptides comprising a β-alanine spacer can be considered a unique aspect of the invention apart from, for example, GLP-2 peptides comprising a gamma-aminobutyric acid (GABA) spacer and/or GLP-2 peptides comprising a γ-glutamic acid spacer.

Each lipophilic substituent typically contains a functional group which may be attached to a functional group of an amino acid of the parent GLP-2 peptide. For example, a lipophilic substituent may contain a carboxyl group which can be attached to an amino group of the parent GLP-2 peptide by means of an amide bond.

As discussed elsewhere herein, the spacer and GLP-2 peptide or GLP-2 amino acid sequence can be associated in any suitable manner. Thus, for example, in one aspect a carboxyl group of the parent GLP-2 peptide forms an amide bond with an amino group of a spacer, and the carboxyl group of the amino acid or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent, whereas, in another exemplary aspect, an amino group of the parent GLP-2 peptide forms an amide bond with a carboxylic group of a spacer, and an amino group of the spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

In one aspect of the invention the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton. In another aspect of the invention the lipophilic substituent is an straight-chain or branched alkyl group.

In one aspect of the invention the lipophilic substituent is the acyl group of a straight-chain or branched fatty acid. In one aspect of the invention the acyl group of a lipophilic substituent is selected from the group comprising $CH_3(CH_2)_nCO$-, wherein n is 4 to 38, such as $CH_3(CH_2)_6CO$-, $CH_3(CH_2)_8CO$-, $CH_3(CH_2)_{10}CO$-, $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-.

In one aspect of the invention the lipophilic substituent is an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid.

In one aspect of the invention the acyl group of the lipophilic substituent is selected from the group comprising $HOOC(CH_2)_mCO$-, wherein m is 4 to 38, such as $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- and $HOOC(CH_2)_{22}CO$-.

In one aspect of the invention the lipophilic substituent is a group of the formula $CH_3(CH_2)_p((CH_2)_qCOOH)CHNH\text{-}CO(CH_2)_2CO$-, wherein p and q are integers and p+q is an integer of from about 8 to about 40, such as from about 12 to about 35.

In one aspect of the invention the lipophlic substituent is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO$-, wherein r is an integer of from about 10 to about 24.

In one aspect of the invention the lipophilic substituent is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO$-, wherein s is an integer of from about 8 to about 24.

In one aspect of the invention the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO$- wherein t is an integer of from about 8 to about 24.

In one aspect of the invention the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer of from about 8 to about 18.

In one aspect of the invention the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}COCH((CH_2)_2COOH)NH\text{-}CO(CH_2)_wCH_3$, wherein w is an integer of from about 10 to about 16.

In one aspect of the invention the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NH\text{-}CO(CH_2)_xCH_3$, wherein x is an integer of from about 10 to about 16.

In one aspect of the invention the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NHCO(CH_2)_yCH_3$, wherein y is zero or an integer of from about 1 to about 22.

In one aspect of the invention the lipophilic substituent is N-Lithocholoyl.

In one aspect of the invention the lipophilic substituent is N-Choloyl.

A GLP-2 derivative can comprise any suitable number of lipophilic substituents alone or in combination with other associated/conjugated groups/moieties. In one exemplary aspect of the invention the GLP-2 derivative has one lipophilic substituent. In another aspect of the invention the GLP-2 derivative has at least two (e.g., 2, 3, or 4) lipophilic substituents. In a further aspect of the invention the GLP-2 derivative has at least three lipophilic substituents. In yet another aspect of the invention the GLP-2 derivative has at least four lipophilic substituents (e.g., 4, 5, or more).

In one aspect of the invention the GLP-2 derivative is selected from:

S5K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)-GLP-2(1-33);

L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S5K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);

L14K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);

L17K(4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D3E/S5K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/S7K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D8K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/E9K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/M10K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N11K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/T12K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/I13K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L14K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D15K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N16K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(decanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(undecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(dodecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tridecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tetradecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(pentadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(heptadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(eicosanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/A18K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D21K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N24K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); and
D3E/Q28K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33). A GLP-2 compound can contain any suitable combination of such GLP-2 derivatives and/or other GLP-2 compounds (including other GLP-2 derivatives, GLP-2 analogs, and/or GLP-2 peptides).

In a further aspect, the present invention relates to (in the context of the methods and/or compositions of the invention) a GLP-2 derivative in which the C-terminal amino acid residue is present in the form of the amide.

In a further aspect, the present invention relates to a GLP-2 derivative having a lipophilic substituent which can be negatively charged. In one aspect the group which can be negatively charged is a carboxylic acid group.

The inventors have discovered that these and other GLP-2 compounds are useful in inducing, promoting, and/or enhancing physiological responses associated with the treatment and/or prevention of a variety of disorders, most notably in diseases, disorders, or conditions associated with the gastrointestinal system. In one exemplary aspect, the invention provides a method of inducing, promoting, enhancing, and/or otherwise exerting one or more trophic effects on the small and/or large intestines in a mammal (e.g., a human, such as a human infant patient) via stimulation of cell proliferation and/or inhibition of apoptosis induced and/or enhanced by the administration of one or more GLP-2 compounds. GLP-2 compounds may also stimulate enterocyte glucose transport, reduce intestinal permeability and inhibit gastric emptying and gastric acid secretion.

The inventors have determined that GLP-2 compounds (e.g., GLP-2 peptides and derivatives thereof) are useful in the treatment and/or prevention of conditions in infants with immature and/or damaged intestines. In one exemplary aspect, the invention provides a method for the treatment of a premature human infant that comprises administering to the premature human infant a composition comprising an amount of a GLP-2 compound in a concentration and amount sufficient to increase in absorption of nutrients from the intestine of the infant. The GLP-2 compound typically is administered in a concentration of from about 0.001 mg/ml to about 0.5 mg/ml in a volume sufficient to provide a detectable increase in nutrient absorption. In more particular aspects, a GLP-2 compound is administered in a concentration of about 0.005-0.09 mg/ml, such as from about 0.01 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.02 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.03 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.04 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.05 mg/ml to a concentration about 0.08 mg/ml, or such as from about 0.06 mg/ml to a concentration about 0.08 mg/ml.

In a further aspect, the invention provides a method for inducing, promoting, and/or enhancing the absorption of nutrients in a premature human infant and/or inducing, promoting, and/or enhancing the treatment and/or prevention of a gastrointestinal disorder in a premature human infant comprising administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml or less in a volume sufficient to provide a detectable increase in absorption of nutrients from the intestine of the infant, wherein the total

amount of GLP-2 compound administered to the infant ranges from 0.01 about mg/day to about 8 mg/day (e.g., about 0.05-8 mg/day, about 0.1-8 mg/day, about 0.25-8 mg/day, about 0.5-8 mg/day, about 1-8 mg/day, about 2-8 mg/day, about 4-8 mg/day, about 6-8 mg/day, about 0.01-6 mg/day, about 0.01-5 mg/day, about 0.01-4 mg/day, about 0.01-3 mg/day, about 0.05-3 mg/day, about 0.05-4 mg/day, about 0.05-6 mg/day, about 0.1-6 mg/day, about 0.1-4 mg/day, about 0.5-6 mg/day, about 1-6 mg/day, about 1-4 mg/day, etc.).

In more specific aspects, the invention provides a method of inducing, promoting, and/or enhancing the absorption of nutrients in a premature human infant (typically a premature human infant diagnoses as having or of being at substantially risk of developing a condition associated with low or poor absorption of nutrients from the intestine) comprising administering to the premature human infant a composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to less than about 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant, wherein the volume is from about 0.05 ml to about 5 ml, such as from about 0.1 ml to about 4 ml, such as from about 0.1 ml to about 3 ml, such as from about 0.1 ml to about 2 ml, such as from about 0.1 ml to about 1 ml, or such as from about 0.1 ml to about 0.5 ml.

In another particular exemplary aspect, the invention provides a method of inducing, promoting, and/or enhancing the absorption of nutrients and/or treating a gastrointestinal disorder in a premature human infant that comprises administering a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant and/or detectable change in a condition (e.g., a physiological marker) associated with the treatment of a gastrointestinal disorder, wherein the body weight of the premature human infant is about 3 kg or less, such as about 2.5 kg or less, such as about 2.0 kg or less, such as about 1.5 kg or less, such as about 1 kg or less, such as about 0.8 kg or less, such as about 0.7 kg or less, or even about 0.6 kg or less.

In a further aspect, the invention provides a method of inducing, promoting, and/or enhancing the absorption of nutrients and/or treatment of gastrointestinal related condition in a premature human infant comprising administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration of about 0.5 mg/ml or less in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant and/or detectable change in condition associated with treatment of a gastrointestinal disorder, wherein the pharmaceutical composition is administered by continuous injection.

In a further aspect, the invention provides a method of promoting, inducing, and/or enhancing the absorption of nutrients in a premature human infant that comprises administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration of about 0.5 mg/ml or less in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant, wherein the pharmaceutical composition is administered by enteral delivery, such as oral feeding.

In a further aspect, the invention provides a method of promoting, inducing, and/or enhancing the absorption of nutrients in a premature human infant that comprises administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration of about 0.5 mg/ml or less in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant, wherein the pharmaceutical composition is administered by subcutaneous injection.

In yet a further aspect of the invention, the invention provides a method for increasing absorption of nutrients in a premature human infant and/or inducing, promoting and/or enhancing the treatment of a gastrointestinal disorder in a premature human infant that comprises administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml or less in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant and/or a detectable change in a condition associated with the treatment of a , wherein the pharmaceutical composition is administered by intravenous injection.

In an additional aspect of the invention a method for promoting absorption of nutrients in a premature human infant and/or promoting, inducing, and/or enhancing a physiological condition associated with the treatment of a gastrointestinal disorder is provided which comprises administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml in a volume sufficient to provide a detectable increase in absorption of nutrients from the intestine of the infant and/or change in the physiological condition, wherein the pharmaceutical composition is administered by infusion, e.g. for administration by infusion bags. In another aspect, the composition is administered as a stable liquid formulation (e.g., by injection).

In a further aspect of the invention the method for the treatment of a premature human infant comprises administering to the premature human infant a pharmaceutical

composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant, wherein the pharmaceutical composition is a stable liquid formulation.

In a further aspect of the invention the method for the treatment of a premature human infant comprises administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant, wherein the pharmaceutical composition is provided for by dissolving a predetermined amount of lyophilized composition comprising a GLP-2 compound in an aqueous or other pharmaceutically acceptable solution.

In a further aspect of the invention the method for the treatment of a premature human infant comprises administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant, wherein the pharmaceutical composition is provided for by thawing a predetermined amount of frozen composition comprising a GLP-2 compound.

In a further aspect of the invention the method for the treatment of a premature human infant comprises administering to the premature human infant a pharmaceutical composition comprising an amount of a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant, wherein the GLP-2 compound is selected from:

S5K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);

L17K(3-(octanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);

L17K(4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S5K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);

L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D3E/S5K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/S7K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D8K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/E9K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/M10K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N11K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/T12K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/I13K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);

D3E/L14K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D15K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N16K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(decanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(undecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(dodecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tridecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tetradecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(pentadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(heptadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(eicosanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K(4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/A18K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/D21K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/N24K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/Q28K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); GLP-2(1-33), 34R-GLP-2(1-34), A2G-GLP-2(1-33), A2G/34R-GLP-2(1-34), K30R-GLP-2(1-33); S5K-GLP-2(1-33); S7K-GLP-2(1-33); D8K-GLP-2(1-33); E9K-GLP-2(1-33); M10K-GLP-2(1-33); N11K-GLP-2(1-33); T12K-GLP-2(1-33); I13K-GLP-2(1-33); L14K-GLP-2(1-33); D15K-GLP-2(1-33); N16K-GLP-2(1-33); L17K-GLP-2(1-33); A18K-GLP-2(1-33); D21K-GLP-2(1-33); N24K-GLP-2(1-33); Q28K-GLP-2(1-33); S5K/K30R-GLP-2(1-33); S7K/K30R-GLP-2(1-33); D8K/K30R-GLP-2(1-33); E9K/K30R-GLP-2(1-33); M10K/K30R-GLP-2(1-33); N11K/K30R-GLP-2(1-33); T12K/K30R-GLP-2(1-33); I13K/K30R-GLP-2(1-33); L14K/K30R-GLP-2(1-33); D15K/K30R-GLP-2(1-33); N16K/K30R-GLP-2(1-33); L17K/K30R-GLP-2(1-33); A18K/K30R-GLP-2(1-33); D21K/K30R-GLP-2(1-33); N24K/K30R-GLP-2(1-33); Q28K/K30R-GLP-2(1-33); K30R/D33K-GLP-2(1-33); D3E/K30R/D33E-GLP-2(1-33); D3E/S5K/K30R/D33E-GLP-2(1-33); D3E/S7K/K30R/D33E-GLP-2(1-33); D3E/D8K/K30R/D33E-GLP-2(1-33); D3E/E9K/K30R/D33E-GLP-2(1-33); D3E/M10K/K30R/D33E-GLP-2(1-33); D3E/N11K/K30R/D33E-GLP-2(1-33); D3E/T12K/K30R/D33E-GLP-2(1-33); D3E/I13K/K30R/D33E-GLP-2(1-33); D3E/L14K/K30R/D33E-GLP-2(1-33); D3E/D15K/K30R/D33E-GLP-2(1-33); D3E/N16K/K30R/D33E-GLP-2(1-33); D3E/L17K/K30R/D33E-GLP-2(1-33); D3E/A18K/K30R/D33E-GLP-2(1-33); D3E/D21K/K30R/D33E-GLP-2(1-33); D3E/N24K/K30R/D33E-GLP-2(1-33); and D3E/Q28K/K30R/D33E-GLP-2(1-33); and combinations of any thereof. Of course, the use of each of these GLP-2 compounds in the various methods of the invention can each be considered a unique aspect of the invention.

The various formulations described in the foregoing methods are also, in and of themselves, independently important features of the invention. Thus, for example, one aspect of the invention is a pharmaceutically acceptable composition, formulated for administration to a premature human infant by subcutaneous injection, continuous injection, or infusion.

In a more particular aspect, the invention provides a lyophilized composition comprising a GLP-2 composition in a concentration of about 0.001 mg/ml to about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients (as typically determined by comparison with a predetermined standard derived from the average absorption in infants having otherwise similar characteristics such as age, etc.) from the intestine and optionally, a pharmaceutically acceptable carrier (desirably a pharmaceutically acceptable carrier that is suitable for administration to infants).

In still another aspect, the invention provides a composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant (preferably where the premature human infant is diagnosed as being unable to absorb sufficient amount of nutrients from the intestine) and, optionally, a pharmaceutically acceptable carrier. In more particular aspects, the invention provides such a composition wherein the concentration of the GLP-2 compound is about 0.005 mg/ml to about 0.09 mg/ml, such as from about 0.01 mg/ml to about 0.08 mg/ml, such as from about 0.02 mg/ml to a about 0.08 mg/ml, such as from about 0.03 mg/ml to about 0.08 mg/ml, such as from about 0.04 mg/ml to about 0.08 mg/ml, such as from about 0.05 mg/ml to about 0.08 mg/ml, or such as from about 0.06 mg/ml to about 0.08 mg/ml.

In a further aspect the pharmaceutical composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients from the intestine and optionally, a pharmaceutically acceptable carrier, is a composition, wherein the amount of a GLP-2 compound is present in an amount sufficient to provide a dosage of about 0.01 to about 8 mg/day (e.g., about 0.05-8 mg/day, about 0.1-8 mg/day, about 0.5-8 mg/day, about 1-8 mg/day, about 2-8 mg/day, about 4-8 mg/day, about 0.1-5 mg/day, about 0.1-3 mg/day, about 0.1-2 mg/day, about 0.1-1 mg/day, etc.).

In a further aspect the pharmaceutical composition comprising a GLP-2 compound (the "GLP-2 compound composition") comprises a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant (typically to provide an increase in nutrient absorption in an infant, premature or otherwise, that has been identified as being unable to absorb sufficient amount of nutrients from the intestine) and optionally, a pharmaceutically acceptable carrier. Typically, the volume of the GLP-2 compound in the GLP-2 compound

composition is about 0.05 ml to about 5 ml, such as from about 0.1 ml to about 4 ml, such as from about 0.1 ml to about 3 ml, such as from about 0.1 ml to about 2 ml, such as from about 0.1 ml to about 1 ml, or such as from about 0.1 ml to about 0.5 ml.

In a further aspect, the invention provides a GLP-2 compound composition wherein the concentration of GLP-2 compound in the composition is about 0.001 mg/ml to about 0.1 mg/ml and the volume of the composition in a dose provides a sufficient amount of the GLP-2 compound to provide a detectable increase in absorption of nutrients from the intestine of a premature human infant (typically having a condition associated with poor absorption of nutrients from the intestine) that is less than about 3 kg, such as below about 2.5 kg, such as below about 2.0 kg, such as below about 1.5 kg, such as below about 1 kg, such as below 0.8 kg, such as below 0.7 kg, or such as below 0.6 kg in weight.

In a further aspect the invention provides a pharmaceutical composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients from the intestine and optionally, a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is formulated for administration by continuous injection.

In a further aspect the invention provides a pharmaceutical composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients from the intestine and optionally, a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is formulated for administration by subcutaneous injection.

In a further aspect the invention provides a pharmaceutical composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients from the intestine and optionally, a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is formulated for administration by intravenous injection.

In a further aspect the pharmaceutical composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to a concentration lower than 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients from the intestine and optionally, a pharmaceutically acceptable carrier is a composition wherein the pharmaceutical composition is formulated for administration by infusion.

In a further aspect the invention provides a pharmaceutical composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant unable to absorb sufficient amount of nutrients from the intestine and optionally, a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a stable liquid formulation.

In a further aspect the invention provides a pharmaceutical composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of a premature human infant (typically in an infant unable to absorb sufficient amount of nutrients from the intestine) and optionally, a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a frozen composition that can be administered upon thawing without significant loss in activity of the GLP-2 compound in terms of increasing nutrient absorption.

In more particular aspects, the invention provides a composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.1 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of an infant (e.g., in a premature human infant unable to absorb sufficient amount of nutrients from the intestine) and optionally, a pharmaceutically acceptable carrier, wherein the GLP-2 compound is selected from:

S5K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)-GLP-2(1-33);

L17K(3-(tridecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);

D21K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S5K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);

L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D3E/S5K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/S7K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D8K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/E9K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/M10K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N11K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/T12K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/I13K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L14K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D15K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N16K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K(3-(decanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(undecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(dodecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tridecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tetradecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(pentadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(heptadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(eicosanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K(4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/A18K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D21K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N24K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/Q28K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); GLP-2(1-33), 34R-GLP-2(1-34), A2G-GLP-2(1-33), A2G/34R-GLP-2(1-34), K30R-GLP-2(1-33); S5K-GLP-2(1-33); S7K-GLP-2(1-33); D8K-GLP-2(1-33); E9K-GLP-2(1-33); M10K-GLP-2(1-33); N11K-GLP-2(1-33); T12K-GLP-2(1-33); I13K-GLP-2(1-33); L14K-GLP-2(1-33); D15K-GLP-2(1-33); N16K-GLP-2(1-33); L17K-GLP-2(1-33); A18K-GLP-2(1-33); D21K-GLP-2(1-33); N24K-GLP-2(1-33); Q28K-GLP-2(1-33); S5K/K30R-GLP-2(1-33); S7K/K30R-GLP-2(1-33); D8K/K30R-GLP-2(1-33); E9K/K30R-GLP-2(1-33); M10K/K30R-GLP-2(1-33); N11K/K30R-GLP-2(1-33); T12K/K30R-GLP-2(1-33); I13K/K30R-GLP-2(1-33); L14K/K30R-GLP-2(1-33); D15K/K30R-GLP-2(1-33); N16K/K30R-GLP-2(1-33); L17K/K30R-GLP-2(1-33); A18K/K30R-GLP-2(1-33); D21K/K30R-GLP-2(1-33); N24K/K30R-GLP-2(1-33); Q28K/K30R-GLP-2(1-33); K30R/D33K-GLP-2(1-33);D3E/K30R/D33E-GLP-2(1-33); D3E/S5K/K30R/D33E-GLP-2(1-33); D3E/S7K/K30R/D33E-GLP-2(1-33); D3E/D8K/K30R/D33E-GLP-2(1-33); D3E/E9K/K30R/D33E-GLP-2(1-33); D3E/M10K/K30R/D33E-GLP-2(1-33); D3E/N11K/K30R/D33E-GLP-2(1-33); D3E/T12K/K30R/D33E-GLP-2(1-33); D3E/I13K/K30R/D33E-GLP-2(1-33); D3E/L14K/K30R/D33E-GLP-2(1-33); D3E/D15K/K30R/D33E-GLP-2(1-33); D3E/N16K/K30R/D33E-GLP-2(1-33); D3E/L17K/K30R/D33E-GLP-2(1-33); D3E/A18K/K30R/D33E-GLP-2(1-33); D3E/D21K/K30R/D33E-GLP-2(1-33); D3E/N24K/K30R/D33E-GLP-2(1-33); D3E/Q28K/K30R/D33E-GLP-2(1-33); and combinations of any thereof.

In yet another aspect, the invention provides a "kit" for promoting the absorption of nutrients from the intestine of an infant (e.g., a premature human infant suffering from a condition associated with less than average/optimal absorption of nutrients) comprising a first component that comprises a predetermined lyophilized amount of a GLP-2 compound; and a second component different from the first component comprising a predetermined volume of aqueous solution; wherein mixture of the first and second components results in a liquid composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of an infant, is a kit, wherein the second component contains a preservative (preferably selected from the group consisting of chlorobutanol, benzyl alcohol, benzalkonium chloride and

mixtures of any or all thereof) in an amount to provide a concentration of the preservative in the injection or infusion solution of about 0.001 to about 2 w/v %.

In another additional aspect of the invention a kit for increasing the absorption of nutrients in the intestine is provided which comprises: a first component comprising a predetermined lyophilized amount of a GLP-2 compound, a second component different from the first component comprising a predetermined volume of aqueous solution; whereby mixture of the first and second components results in a liquid composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant. In one embodiment of the invention this is a kit, wherein the concentration of the GLP-2 compound is from about 0.005 mg/ml to a concentration about 0.09 mg/ml, such as from about 0.01 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.02 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.03 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.04 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.05 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.06 mg/ml to a concentration about 0.08 mg/ml. In one embodiment the second component is water devoid of any further component having a function.

In a further aspect, the invention provides a kit for preparing a medicament for increasing the absorption of nutrients in an infant (such as a premature human infant suffering from a condition associated with impaired nutrient absorption) comprising a first component comprising a predetermined lyophilized amount of a GLP-2 compound; and a second component different from the first component comprising a predetermined volume of aqueous solution; whereby mixture of the first and second components results in a liquid composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant and wherein the volume of the medicament is from about 0.05 ml to about 5 ml, such as from about 0.1 ml to about 4 ml, such as from about 0.1 ml to about 3 ml, such as from about 0.1 ml to about 2 ml, such as from about 0.1 ml to about 1 ml, or such as from about 0.1 ml to about 0.5 ml.

The invention also provides a kit for preparing a pharmaceutical composition/medicament useful in increasing absorption of nutrients in an infant and/or promoting, inducing, and/or enhancing the treatment or prevention of a gastrointestinal disorder in an infant comprising a first component comprising a predetermined lyophilized amount of a GLP-2 compound; a second component different from the first component comprising a predetermined volume of aqueous solution; whereby mixture of the first and second

components results in a liquid composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml in a volume sufficient to provide an increase in absorption of nutrients from the intestine of the infant and wherein the GLP-2 compound is selected from:

S5K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);

L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S5K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)/K30R-GLP-2(1-33);

L17K(3-(nonanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);

L17K(4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D3E/S5K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/S7K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D8K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/E9K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/M10K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N11K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/T12K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/I13K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L14K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D15K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N16K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(decanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(undecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(dodecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tridecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tetradecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(pentadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(heptadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(eicosanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/A18K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D21K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N24K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/Q28K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); GLP-2(1-33), 34R-GLP-2(1-34), A2G-GLP-2(1-33), A2G/34R-GLP-2(1-34), K30R-GLP-2(1-33); S5K-GLP-2(1-33); S7K-GLP-2(1-33); D8K-GLP-2(1-33); E9K-GLP-2(1-33); M10K-GLP-2(1-33); N11K-GLP-2(1-33); T12K-GLP-2(1-33); I13K-GLP-2(1-33); L14K-GLP-2(1-33); D15K-GLP-2(1-33); N16K-GLP-2(1-33); L17K-GLP-2(1-33); A18K-GLP-2(1-33); D21K-GLP-2(1-33); N24K-GLP-2(1-33); Q28K-GLP-2(1-33); S5K/K30R-GLP-2(1-33); S7K/K30R-GLP-2(1-33); D8K/K30R-GLP-2(1-33); E9K/K30R-GLP-2(1-33); M10K/K30R-GLP-2(1-33); N11K/K30R-GLP-2(1-33); T12K/K30R-GLP-2(1-33); I13K/K30R-GLP-2(1-33); L14K/K30R-GLP-2(1-33); D15K/K30R-GLP-2(1-33); N16K/K30R-GLP-2(1-33); L17K/K30R-GLP-2(1-33); A18K/K30R-GLP-2(1-33); D21K/K30R-GLP-2(1-33); N24K/K30R-GLP-2(1-33); Q28K/K30R-GLP-2(1-33); K30R/D33K-

GLP-2(1-33); D3E/K30R/D33E-GLP-2(1-33); D3E/S5K/K30R/D33E-GLP-2(1-33); D3E/S7K/K30R/D33E-GLP-2(1-33); D3E/D8K/K30R/D33E-GLP-2(1-33); D3E/E9K/K30R/D33E-GLP-2(1-33); D3E/M10K/K30R/D33E-GLP-2(1-33); D3E/N11K/K30R/D33E-GLP-2(1-33); D3E/T12K/K30R/D33E-GLP-2(1-33); D3E/I13K/K30R/D33E-GLP-2(1-33); D3E/L14K/K30R/D33E-GLP-2(1-33); D3E/D15K/K30R/D33E-GLP-2(1-33); D3E/N16K/K30R/D33E-GLP-2(1-33); D3E/L17K/K30R/D33E-GLP-2(1-33); D3E/A18K/K30R/D33E-GLP-2(1-33); D3E/D21K/K30R/D33E-GLP-2(1-33); D3E/N24K/K30R/D33E-GLP-2(1-33); D3E/Q28K/K30R/D33E-GLP-2(1-33); and combinations of any thereof.

The GLP-2 compound is preferably a GLP-2 peptide, a nucleic acid encoding a GLP-2 peptide, a vector comprising such a nucleic acid, or a host cell comprising such a nucleic acid or vector. GLP-2 peptides, per se (e.g., GLP-2 derivatives), are particularly preferred GLP-2 compounds in most method and composition aspects of the invention.

GLP-2 peptides can be produced by any suitable method. For example, a GLP-2 peptide (or parent GLP-2 peptide in the case of a GLP-2 derivative) can be prepared by a method which comprises culturing a host cell containing a DNA sequence encoding the GLP-2 peptide and capable of expressing the GLP-2 peptide in a suitable nutrient medium under conditions permitting the expression of the GLP-2 peptide, after which the resulting GLP-2 peptide is recovered from the culture.

The medium used to culture the cells may be any conventional medium suitable for growing the host cells, such as minimal or complex media containing appropriate supplements. Suitable media are available from commercial suppliers or may be prepared according to published recipes (*e.g.* in catalogues of the American Type Culture Collection). The GLP-2 peptide produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, *e.g.* ammonium sulphate, purification by a variety of chromatographic procedures, *e.g.* ion exchange chromatography, gel filtration chromatography, affinity chromatography, or the like, dependent on the type of GLP-2 peptide in question.

A nucleic acid sequence encoding the GLP-2 peptide can be any suitable sequence, such as a genomic DNA sequence or cDNA sequence encoding a GLP-2 peptide, which, for instance, can be obtained by preparing a genomic or cDNA library and screening for DNA sequences coding for all or part of the desired GLP-2 peptide by hybridization using synthetic oligonucleotide probes in accordance with standard techniques (see, for example, Sambrook, J, Fritsch, EF and Maniatis, T, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor

Laboratory Press, New York, 1989). A DNA or other nucleic acid sequence encoding the GLP-2 peptide may also be prepared synthetically by established standard methods, *e.g.* the phosphoamidite method described by Beaucage and Caruthers, *Tetrahedron Letters* 22 (1981), 1859 - 1869, or the method described by Matthes *et al.*, *EMBO Journal* 3 (1984), 801 - 805. A DNA sequence also may also be prepared by polymerase chain reaction using specific primers, for instance as described in US 4,683,202 or Saiki *et al.*, *Science* 239 (1988), 487 - 491.

A GLP-2 encoding DNA sequence or other suitable GLP-2 encoding nucleic acid sequence may be inserted into any suitable vector (preferably which may conveniently be subjected to recombinant DNA procedures). The choice of vector often depends on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, *i.e.* a vector which exists as an extrachromosomal entity, the replication of which typically is independent of chromosomal replication, *e.g.* a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

A vector comprising a GLP-2 peptide-encoding nucleic acid sequence is preferably an expression vector in which a DNA sequence encoding a GLP-2 peptide is operably linked to additional sequences/segments useful in or required for transcription of the GLP-2 peptide-encoding sequence, such as a promoter, an enhancer, a Kozak consensus sequence, etc. A promoter can be any DNA sequence which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the DNA encoding the GLP-2 peptide of the invention in a variety of host cells are well known in the art, cf. for instance Sambrook *et al.*, *supra*.

A DNA sequence encoding the GLP-2 peptide may also, if necessary, be operably connected to a suitable terminator, polyadenylation signal(s), transcriptional enhancer sequences, and translational enhancer sequences. A recombinant vector of the invention may further comprise a DNA sequence enabling the vector to replicate in the host cell in question.

A vector may also comprise a selectable marker, *e.g.* a gene the product of which complements a defect in the host cell or one which confers resistance to a drug, *e.g.* ampicillin, kanamycin, tetracycline, chloramphenicol, neomycin, hygromycin, and/or methotrexate.

To facilitate directing the GLP-2 peptide (e.g., a parent GLP-2 peptide intermediate in the production of a GLP-2 derivative) into the secretory pathway of the host cells, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) may be provided in the recombinant vector. A secretory signal sequence typically is included in a GLP-2 peptide-encoding DNA in the correct reading frame and located 5' to the DNA sequence

encoding the GLP-2 peptide. A secretory signal sequence may be a sequence that is normally associated with a GLP-2 peptide or may correspond to another (non-GLP-2) secreted protein.

The procedures used to ligate DNA peptide-coding sequences (e.g., a sequence coding for one or more GLP-2 peptides), promoters, terminators and/or secretory signal sequences, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook *et al.., supra*).

The host cell into which the DNA sequence or the recombinant vector is introduced may be any cell which is capable of producing the present GLP-2 peptides, such as bacteria, yeast, fungi and higher eukaryotic cells. Examples of suitable host cells well known and used in the art are, without limitation, *E. coli*, *Saccharomyces cerevisiae*, and mammalian BHK or CHO cell lines.

GLP-2 derivatives of the invention can be prepared by introducing the lipophilic substituent into the parent GLP-2 peptide using methods known *per se*, see for example WO 95/07931, the contents of which is hereby incorporated in its entirety by reference.

N^{ε}-acylation of a Lys residue can be carried out by using an activated amide of the acyl group to be introduced as the acylating agent, *e.g.* the amide with benzotriazole. The acylation can be carried out in a polar solvent in the presence of a base.

Pharmaceutical compositions containing a GLP-2 compound can be administered by any suitable route of administration and in any suitable form, a number examples of which are provided elsewhere herein.

In certain aspects, a GLP-2 compound composition is administered parenterally to patients in need of treatment with the GLP-2 compound (e.g., infants afflicted with a condition associated with poor nutrient absorption from the intestine). Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. GLP-2 compound compositions formulated for such forms of delivery are important aspects of the invention.

In another aspect, the invention provides a pharmaceutically acceptable composition comprising a GLP-2 compound (in an amount sufficient to promote, induce, and/or enhance a desired physiological effect in a mammal, such as in a premature human infant) wherein the composition is in the form of a powder or a liquid for the administration nasal or pulmonary administration (e.g., as a nasal spray).

In other aspects, the invention provides a GLP-2 compound composition that is formulated for transdermal administration. For example, in one aspect the invention provides a

GLP-2 compound composition that is contained in a drug-in-matrix, drug-in-reservoir, iontophoretic, or other suitable type of "patch" for transmission across the skin. In other aspects, the invention provides a GLP-2 compound composition that is formulated for buccal and/or transmucosal administration. A composition for nasal administration of GLP-2 may, for example, be prepared as described in European Patent No. 272097 (to Novo Nordisk A/S) or in WO 93/18785.

For the most part, pharmaceutically acceptable formulations containing a GLP-2 compound for administration to a patient may be prepared by conventional techniques, *e.g.* as described in Remington's Pharmaceutical Sciences, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995. Thus, for example, an injectable composition of a GLP-2 compound can be prepared using the conventional technique of dissolving and mixing the ingredients of the composition, as appropriate, to obtain a desired end product composition. Thus, according to one exemplary procedure, a GLP-2 compound is dissolved in an amount of water which is somewhat less than the final volume of the composition to be prepared. An isotonic agent, a preservative, and a buffer are added as desired and the pH value of the solution is adjusted - if necessary - using an acid, *e.g.* hydrochloric acid, or a base, *e.g.* aqueous sodium hydroxide as desired. Finally, the volume of the solution is adjusted with water to give the desired concentration of the ingredients. Examples of isotonic agents are sodium chloride, mannitol and glycerol. Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate, and benzyl alcohol. Examples of suitable buffers are sodium acetate and sodium phosphate. Further to the above-mentioned components, solutions containing a GLP-2 compound according to the present invention may also contain a surfactant in order to improve the solubility and/or the stability of the receptor agonist.

The pharmacological properties of the compounds of the invention can be tested *e.g.* as described in International Patent Application No. PCT/DK97/00086, WO 97/31943.

In a further aspect the invention relates to a pharmaceutical formulation comprising a GLP-2 compound and a buffer, wherein the GLP-2 compound is present in a concentration from about 0.001 mg/ml to about 0.1 mg/ml (e.g., about 0.05-0.1 mg/ml, about 0.005-0.1 mg/ml, about 0.01-0.1 mg/ml, etc.), and wherein the formulation has a pH from about 8 to about 10 (e.g., about 8.5-9.5).

In a further aspect, the invention relates to a pharmaceutical formulation comprising an aqueous solution of a GLP-2 compound and a buffer, wherein the GLP-2 compound is present in a concentration from about 0.001 mg/ml to about 0.1 mg/ml (e.g., about 0.05-0.1 mg/ml, about 0.005-0.1 mg/ml, or about 0.01-0.1 mg/ml), and wherein the formulation has a pH from about 8.0 to about 10 (e.g., about 8.5-9.5).

In a further aspect the invention relates to a method of preparing a physically stable pharmaceutical formulation of a GLP-2 compound comprising preparing a formulation containing the GLP-2 compound, and a buffer, wherein the GLP-2 compound is present in a concentration from about 0.001 mg/ml to about 0.1 mg/ml, and wherein the formulation has a pH from about 8.0 to about 10.

In a further aspect the invention relates to a method of preparing a physically stable pharmaceutical formulation of a GLP-2 compound comprising preparing an aqueous solution containing the GLP-2 compound, and a buffer, wherein the GLP-2 compound is present in a concentration from about 0.001 mg/ml to about 0.1 mg/ml, and wherein the formulation has a pH from about 8.0 to about 10.

In a further aspect the invention relates to a method of preparing a physically stable pharmaceutical formulation of a GLP-2 compound comprising preparing a formulation containing the GLP-2 compound, water, and a buffer, wherein the GLP-2 compound is present in a concentration from about 0.001 mg/ml to about 0.1 mg/ml, and wherein the formulation has a pH from about 8.0 to about 10.

In another aspect, the invention provides a method for inducing, promoting, and/or enhancing one or more physiological responses in a mammal (e.g., a human patient) associated with the treatment or prevention of intestinal failure or other condition leading to malabsorption of nutrients in the intestine, comprising administering to a patient in need thereof an effective amount of a pharmaceutically acceptable composition comprising an aqueous solution of a GLP-2 compound, and a buffer, wherein the GLP-2 compound is present in a concentration from about 0.001 mg/ml to about 0.1 mg/ml (e.g., about 0.05-0.1 mg/ml, about 0.005-0.1 mg/ml, about 0.001-0.01 mg/ml, about 0.005-0.01 mg/ml, about 0.001-0.05 mg/ml, etc.).

The term "an effective amount" refers to a dose determined to be effective by a qualified practitioner , who may titrate dosages to achieve the desired response, body of practitioners, and/or regulatory agency (the latter two cases typically being determined for a population of patients having a similar set of conditions). Factors for consideration of dose can include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, condition of treatment (e.g. diabetes, obesity, weight loss, gastric ulcers, Crohn's disease, GERD, etc.), patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g., insulin, an EGF, a keratinocyte growth factor (KGF – such as KGF-2 or an analog or derivative thereof), a growth hormone (e.g., hGH), an insulin-like growth factor (e.g., IGF-1 and/or IGF-2), a vascular endothelial growth factor (VEGF), a fibroblast growth factor (FGF), etc. (and related nucleic acids, vectors, and cells) each of

which and/or combinations thereof can be suitable additional medicaments for administration in methods described herein), time of administration, or other factors known to medical practitioners.

Also some nutrients such as glutamine, arginine, omega-3 fatty acids, and probiotics have been shown to influence intestinal barrier function and immune system and it is therefore an aspect of the present invention to treat premature human infants with a GLP-2 compound in combination with nutritional supplements by enteral or parenteral intake.

Thus, in one aspect, the invention relates to a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound in combination with a further compound selected from the group consisting of glutamine, arginine, glycine, histidine, taurine, and tyrosine.

In a further aspect, the invention relates to a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound in combination with a further compound selected from the group consisting of surfactant, such as Survanta® (beractant) and/or Exosurf® ((Colfosceril palmitate, Cetyl Alcohol, Tyloxapol), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and Erythropoietin (EPO).

In a further aspect, the invention relates to a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound, wherein said composition do not contain any further peptide hormone.

In a further aspect, the invention relates to a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound, wherein said composition do not contain any further compound selected from the group consisting of Insulin-like Growth Factor 1 (IGF-1), analogs of IGF-1, Insulin-like Growth Factor 2 (IGF-2), analogs of IGF-2, Growth Hormone (GH), and analogs of GH.

In a further aspect, the invention relates to a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition

comprising a GLP-2 compound, wherein said composition do not contain a Keratinocyte Growth Factor (KGF) protein.

In a further aspect, the invention relates to a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound, wherein said composition do not contain a Dipeptidyl Peptidase IV (DPP-IV) inhibitor.

In a further aspect, the invention relates to a method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound, wherein said composition do not contain a GLP-1 activity inhibitor, such as exendin(9-39). "GLP-1 activity inhibitor" means an agent or compound or treatment modality, that inhibits GLP-1 activity *in vivo*.

In certain aspects, a GLP-2 compound (such as a GLP-2 peptide – e.g., a GLP-2 peptide derivative) is administered in the form of an aqueous pharmaceutically acceptable formulation - i.e. a formulation comprising water (such formulations also are, in and of themselves, important aspects of the invention). Such a formulation is typically a solution or a suspension. In a further aspect of the invention the pharmaceutical formulation is an aqueous solution. The term "aqueous formulation" is defined as a formulation comprising at least 50 % w/w water. The term "aqueous solution" is defined as a solution comprising at least 50 % w/w water, and the term "aqueous suspension" is defined as a suspension comprising at least 50 % w/w water.

A pharmaceutical formulation of a GLP-2 compound also can be in the form a freeze-dried formulation, whereto the physician or the patient adds a solvent prior to administration. In another aspect the invention provides a pharmaceutical formulation comprising a GLP-2 compound that is a lyophilized formulation whereto the physician or the patient adds a solvent prior to use.

A pharmaceutical formulation is found to be physically unstable when it exhibits turbidity. Stable GLP-2 compound formulations of the invention may be physically stable for more than about 3 months, more than about 6 months, more than about 9 months, more than about 10 months, more than about 11 months, more than about one year, more than about 18 months, more than about 22 months, or even more than about two years at temperatures of about 5°C or less.

Physical stability of the formulations can be evaluated by means of visual inspection and evaluating turbidity after storage of the formulation at different temperatures in top filled

glass cartridges for various time periods. Visual inspection of the formulations can be performed, for example, in a sharp focused light with a dark background. The turbidity of the formulation can be characterized by a visual score ranking the degree of turbidity from 0 to about 3 (a formulation showing no turbidity corresponds to a visual score of 0, and a formulation showing visual turbidity in daylight corresponds to visual score of 3). A formulation can be classified as physical unstable with respect to protein aggregation, when it shows visual turbidity in daylight.

GLP-2 compound pharmaceutical formulations of the invention advantageously can remain physically stable for at least about 6 weeks, at least about 9 weeks, more than about 12 weeks, more than about 6 months, more than about one year, more than about 15 months, or longer at temperatures of about 5°C or less, as measured by stability tests known to the person skilled in the art and as approved by regulatory authorities. Stability method references that may be used as guides for analytical method validation include "Stability of Pharmaceutical Products" *Remington's Pharmaceutical Sciences*, 1985. It is appropriate to note that some specific stability tests are often indicated for certain pharmaceutical dosage forms in addition to those normally conducted.

GLP-2 compound formulations of the invention also advantageously retain physical stability at higher temperatures. For example, GLP-2 formulations of the invention can retain physical stability for about 6 weeks or longer, about 9 weeks or longer, about 12 weeks or longer at temperatures of about 25°C or less (e.g., temperatures of about 5-25°C, temperatures of about 10-25°C, temperatures of about 15-25°C, or temperatures of about 20-25°C).

The inventors have determined that the pH of a GLP-2 compound formulation can impact the usefulness of the formulation in treatment (e.g., in increasing nutrient absorption in a premature human infant). Thus, for example, in one aspect the invention provides a GLP-2 formulation has a pH in the range from about 7.6 to about 10; in another aspect the GLP-2 composition has a pH of about 7.7 to about 10; in a further aspect the invention provides a formulation has a pH in the range from about 7.8 to about 10. In yet another aspect, the invention provides a formulation having a pH of about 7.9 to about 10. In additional aspects, the invention provides GLP-2 compound formulations having a pH of about 8.0 to about10, about 8.0 to about 9.5, about 8 to about 9, about 8 to about 8.5, about 8.5 to about 10, about 8.5 to about 9.5, about 8.5 to about 9, about 9 to about 10, about 9 to about 9.5, or about 9.5 to about 10.

In a further aspect of the invention the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine,

sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), N,N-bis-(2-hydroxyethyl)-glycin (BICIN), Diammonium hydrogen phosphate ($(NH_4)_2HPO_4$) and tris(hydroxymethyl)-aminomethan, or mixtures thereof. Each one of these specific buffers constitutes an alternative aspect of the invention. In a further aspect of the invention the buffer is glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures of any or all thereof.

In another aspect, the invention provides a GLP-2 compound formulation that also or alternatively comprises a pharmaceutically acceptable preservative. GLP-2 compound formulations can include any suitable preservative. Examples of preservatives include phenol, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures of any or all thereof. Formulations comprising each of these specific preservatives constitutes an alternative aspect of the invention. In a preferred aspect of the invention the preservative is phenol or m-cresol.

Where the invention provides a GLP-2 compound formulation comprising a preservative, the preservative can be present in any suitable amount. Typically, in such formulations, the preservative component is present in a concentration from 0.1 mg/ml to 20 mg/ml. In a further aspect of the invention the preservative is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further aspect of the invention the preservative is present in a concentration from 5 mg/ml to 10 mg/ml. In a further aspect of the invention the preservative is present in a concentration from 10 mg/ml to 20 mg/ml. Formulations comprising each one of these specific concentration ranges constitute alternative aspects of the invention.

The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further aspect of the invention the formulation further comprises an isotonic agent. In a further aspect of the invention the isotonic agent is selected from the group consisting of a salt (e.g. sodium chloride), a polyhydric alcohol (e.g. propyleneglycol, xylitol, mannitol, sorbitol or glycerol), a monosaccharide (e.g. glucose or maltose), a disccharide (e.g. sucrose), an amino acid (e.g. L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine), polyethyleneglycol (e.g. PEG400), or mixtures thereof. In a further aspect of the invention the isotonic agent is selected from the group consisting of sodium chloride, glycerol, mannitol, glucose, sucrose, L-glycine, L-histidine, arginine, lysine or mixtures thereof. Each one of these specific isotonic agents constitutes an alternative

aspect of the invention. In one aspects of the invention the isotonic agent is mannitol. In one aspects of the invention the isotonic agent is glycerol. In one aspects of the invention the isotonic agent is sucrose.

In a further aspect of the invention the isotonic agent is present in a concentration from about 1 mg/ml to about 50 mg/ml. In a further aspect of the invention the isotonic agent is present in a concentration from about 1 mg/ml to about 7 mg/ml. In a further aspect of the invention the isotonic agent is present in a concentration from about 8 mg/ml to about 16 mg/ml. In a further aspect of the invention the isotonic agent is present in a concentration from about 17 mg/ml to about 50 mg/ml. Each one of these specific concentration ranges constitutes an alternative aspect of the invention.

The use of an isotonic agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further aspect of the invention the formulation further comprises a chelating agent. Any suitable chelating agent can be included in such formulations. In one exemplary aspect, the chelating agent is selected from salts of ethylenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof. Each one of these specific chelating agents constitutes an alternative aspect of the invention.

When present in a formulation of the invention, the chelating agent can be present in any suitable amount. In an exemplary aspect, the chelating agent is present in a concentration from about 0.1mg/ml to about 5mg/ml. In a further aspect of the invention the chelating agent is present in a concentration from about 0.1mg/ml to about 2mg/ml. In a further aspect of the invention the chelating agent is present in a concentration from about 2mg/ml to about 5mg/ml.

The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further aspect of the invention the formulation further comprises a stabilizer selected from the group of high molecular weight polymers or low molecular compounds. In a further aspect of the invention the stabilizer is selected from polyethylene glycol (e.g. PEG 3350), polyvinylalcohol (PVA), polyvinylpyrrolidone, carboxymethylcellulose, different salts (e.g. sodium chloride), L-glycine, L-histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and mixtures thereof. Each one of these specific stabilizers constitutes an alternative aspect of the invention. In a preferred aspect of the invention the stabilizer is selected from the group consisting of L-histidine, imidazole and arginine.

In a further aspect of the invention a high molecular weight polymer is present in a concentration from about 0.1mg/ml to about 50mg/ml. In a further aspect of the invention the high molecular weight polymer is present in a concentration from about 0.1mg/ml to about 5mg/ml. In a further aspect of the invention the high molecular weight polymer is present in a concentration from about 5mg/ml to about 10mg/ml. In a further aspect of the invention the high molecular weight polymer is present in a concentration from about 10mg/ml to about 20mg/ml. In a further aspect of the invention the high molecular weight polymer is present in a concentration from about 20mg/ml to about 30mg/ml. In a further aspect of the invention the high molecular weight polymer is present in a concentration from about 30mg/ml to about 50mg/ml.

In a further aspect of the invention a low molecular weight compound is present in a concentration from about 0.1mg/ml to about 50mg/ml. In a further aspect of the invention the low molecular weight compound is present in a concentration from about 0.1mg/ml to about 5mg/ml. In a further aspect of the invention the low molecular weight compound is present in a concentration from about 5mg/ml to about 10mg/ml. In a further aspect of the invention the low molecular weight compound is present in a concentration from 10mg/ml to 20mg/ml. In a further aspect of the invention the low molecular weight compound is present in a concentration from about 20mg/ml to about 30mg/ml. In a further aspect of the invention the low molecular weight compound is present in a concentration from about 30mg/ml to about 50mg/ml.

The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In a further aspect of the invention the formulation further comprises a surfactant. In a further aspect of the invention the surfactant is selected from a detergent, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxylated derivatives (tweens, e.g. Tween-20, or Tween-80), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glyceroglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, CAS registry no [577-11-7]), docusate calcium, CAS registry no [128-49-4]), docusate potassium, CAS registry no [7491-09-0]), SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl phosphatidic

acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)- derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (e.g. N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β-D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives- (e.g. sodium tauro-dihydrofusidate etc.), long-chain fatty acids and salts thereof C6-C12 (e.g. oleic acid and caprylic acid), acylcarnitines and derivatives, N^{α}-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N^{α}-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N^{α}-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof. Each one of these specific surfactants constitutes an alternative aspect of the invention.

The use of a surfactant in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In one aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is free of one or more of the aforementioned excipients. For example, in one aspect, the invention provides pharmaceutically acceptable formulations consisting or consisting essentially of a GLP-2 compound in a sterile pyrogen-free solution comprising bacteriostatic water. The invention also provides a kit comprising such agents, which also may include assay materials for stability, toxicity, dose, etc.

In another aspect, the invention provides pharmaceutical formulations wherein the primary active ingredient, if not essentially only active ingredient, is a GLP-2 compound. In another aspect, the invention provides pharmaceutically acceptable formulations wherein a GLP-2 compound is the primary isolated active ingredient, if not the only detectable isolated active ingredient (e.g., the composition may contain unisolated growth hormone, epidermal growth factor, and the like in the form of a nutritional supplement).

In yet another aspect, the invention provides pharmaceutically acceptable formulations wherein an amount of a GLP-2 compound effective for treatment of a premature human infant (neonate), an optional sterile and pyrogen-free diluent, and one or more therapeutic micronutrients and/or other parenteral nutrition agents, such as phosphorus, calcium, etc. are combined (or a composition comprising such nutrients – such as a composition comprising a combination of organic phosphorus and/or calcium phosphate, another calcium salt (e.g., calcium gluconate), and optional other agents, such as L-cysteine hydrochloride, glucose, and/or free amino acids, is combined with or co-administered with the GLP-2 compound). Other agents that might be similarly included in such a formulation include vitamins (A, B1, B2, B6, B12, C, D, E, K, nicacin, biotin, and/or folate), a suitable sodium salt (e.g., sodium acetate), a suitable magnesium salt (e.g., mangesium sulfate), sodium glycerophosphate, heparin sodium, inorganic phosphate (e.g., sodium phosphate), a potassium salt (e.g., potassium chloride), amino acid formulations (e.g., TrophAmine), casein hydrosylates, soy proteins, premature nutritional formula (e.g., Enfamil Premature, Similac Special Care, Pregestimil (Mead Johnson), Alimentum (Ross Labs), NeoCate (SHS North America), etc.), cysteine HCl, trace element (copper, zinc, chromium, manganese, and/or selenium) compositions, dextrose, insulin, albumin, fiber and/or fiber-based nutritional agents (e.g., soy polysaccharide composition, pectin, etc.), glutamine, cow's milk-based nutritional agents, human breast milk compositions (e.g., fortified human breast milk), caloric supplements (e.g., MCT oil, vegetable oil, polycose powder, corn oil, etc.), etner fats (e.g., long-chain fatty acids or medium chain trigylcerides), immunoglobulins, short chain (C_4-C_{10}) fatty acids, electrolytes, molybdenum, carnitine, flouride, elemental iron compositions (e.g., ferrous sulfate elixir), and/or lipid emulsions (e.g., intralipid). The invention also provides kits comprising such agents.

In additional aspects, the invention provides pharmaceutically acceptable formulations which are free of agents that may pose a significant risk of adverse reaction in a premature human infant. In one exemplary aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is free of any presevative. In another exemplary aspect of the invention the pharmaceutical formulation comprising the GLP-2

compound is also or alternatively free of any stabilizer. In yet one more aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is also or alternatively free of any isotonic agent. In one aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is also or alternatively free of any chelating agent. In still another aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is also or alternatively free of any surfactant.

In another aspect, the invention provides a pharmaceutical formulation comprising an effective amount of a GLP-2 compund, wherein the formulation is free of any excipient. Such a composition may nonetheless include suitable diluents, such as sterile water for injection or other non-active carrier, such as a suitable infant formula.

In another aspect, the invention relates to the preparation of a pharmaceutically acceptable composition comprising a GLP-2 compound having any one or combination of the above-described features (e.g., being free of other isolated active agents such as growth hormone, insulin-like growth factor-1, insulin-like growth factor-2, or analogs of any thereof. The method comprises providing a GLP-2 compound composition comprising a GLP-2 compound in a dosage effective for an adult indication, such as for the treatment of SBS, Chron's disease, or the like in an adult human, and formulating the composition for administration (typically intravenous administration by continuous injection or infusion) to a premature human infant by reducing the concentration of the GLP-2 compound to one suitable for treatment of a premature human infant by addition of one or more diluents suitable for administration to a premature human infant (e.g., sterile water) to the adult GLP-2 compound composition. Typically, such a method will involve the reduction of concentration of a GLP-2 compound composition comprising from about 1-50 mg of GLP-2 compound, such as about 2-40 mg of GLP-2 compound, such as about 3-20 mg of GLP-2 compound (e.g., about 5-20 mg), to a concentration of about 0.01-10 mg, typically less than about 2 mg, more typically less than about 1 mg, still more typically less than about 0.5 mg, even more typically less than about 0.2 mg, or less than about 0.1 mg, such as less than about 0.05 mg (e.g., less than about 0.025 mg). The method typically comprises consulting a computer dosage program that considers the weight of the premature human infant or analytical chart that provides the same functionality. The method also may optionally include testing the re-formulated infant composition for toxicity, stability, presence of contaminants, turbidity, and/or tonicity prior to administration. Such testing may be similarly provided by a device comprising a computer system for dosing, as mentioned above. Kits also including testing equipment, dosing equipment, and suitable diluents are provided by the invention. Such methods, kits, programs, and/or devices also can include means for assessing the dosage of

GLP-2 compound in the infant formulation. In one aspect, the inventive method comprises formulating the GLP-2 compound with nutritional supplements and/or micronutrients. In another aspect, the inventive method also or alternatively comprises formulating the GLP-2 compound with a suitable anti-bacterial agent. In one aspect, the method comprises reconstituting a lyophylized GLP-2 composition comprising an adult dosage, as exemplified above. In another aspect, the inventive method also or alternatively comprises removing undesirable agents from the adult GLP-2 compound formulation, such as preservatives that may be potentially harmful to infants. In a further aspect, the inventive method also or alternatively comprises storing the infant GLP-2 compound formulation in a sterile vial or ampuoule suitable for storage and rapid administration via a catheter, IV tube, or other device used to deliver pharmaceutical agents to a premature human infant. In another aspect, the invention provides a method for promoting the sale of suitable carriers for GLP-2 compounds, comprising distributing/disseminating information about the use of such carriers for diluting adult dose GLP-2 formulations and/or kits comprising carriers for such dilution, for the preparation of GLP-2 compound formulations in the treatment of infants. Such information may include suitable doses for treating conditions in infants, stability information, re-formulation instructions, etc., and may be distributed to hospitals, pharmacists, formularies, primary care physicians, nurses, nurse practioners, insurance agencies, formularies, state and/or national regulatory agencies, etc., by means of internet advertising, phone advertising, e-mail marketing, direct mail marketing, hosting of seminars, providing free samples of such products, contacting key opinion leaders regarding such products through the use of liasons, funding publications describing the use of such products, etc.

In one aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is physically stable for more than 12 weeks and for more than 15 months at 5°C as measured by visual inspection.

In another aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is physically stable for more than 12 weeks at 25°C as measured by visual inspection.

In a further aspect of the invention the pharmaceutical formulation comprising the GLP-2 compound is physically stable for more than 12 weeks at 37°C as measured by visual inspection.

In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.0 to 10. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.0 to 9.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from

7.0 to 9.0. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.0 to 8.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.0 to 8.0. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.0 to 7.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.5 to 10. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 8.0 to 10. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 8.5 to 10. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 9.0 to 10. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 9.5 to 10. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.5 to 9.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.5 to 9.0. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.5 to 8.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 7.5 to 8.0. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 8.0 to 9.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 8.0 to 9.0. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 8.0 to 8.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 8.5 to 9.5. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 8.5 to 9.0. In a further aspect of the invention the formulation comprising the GLP-2 compound has a pH in the range from 9.0 to 9.5.

These foregoing features and aspects of the compositions/formulations of the invention can be combined in any suitable manner. An exemplary list of particular formulations including various combinations of such features and aspects that can be useful components of compositions and/or useful in practicing the various methods of the invention is provided here:

a formulation comprising an aqueous solution of 0.01 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.05 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.07 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.1.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.1.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.1.

a formulation comprising an aqueous solution of 0.05 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.1.

a formulation comprising an aqueous solution of 0.07 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.1.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.0

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.0.

a formulation comprising an aqueous solution of 0.05 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.0.

a formulation comprising an aqueous solution of 0.07 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.1.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.1.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.1.

a formulation comprising an aqueous solution of 0.05 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.1.

a formulation comprising an aqueous solution of 0.07 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.1.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 5 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 5 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 5 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 7 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 7 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 7 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycylglycine, 16.0mg/ml glycerol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycylglycine, 16.0mg/ml glycerol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycylglycine, 16.0mg/ml glycerol, and 5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycylglycine, 16.0mg/ml glycerol, and 7 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycylglycine, 16.0mg/ml glycerol, and 7 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycylglycine, 16.0mg/ml glycerol, and 7 mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.0.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 38.5mg/ml mannitol, and either 3mg/ml m-cresol or 1.5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 38.5mg/ml mannitol, and either 3mg/ml m-cresol or 1.5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 38.5mg/ml mannitol, and either 3mg/ml m-cresol or 1.5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 38.5mg/ml mannitol, and either 3mg/ml m-cresol or 1.5mg/ml phenol, at pH 8.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.8.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.8.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.8.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 8.8.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 5mg/ml phenol, and either 1mg/ml EDTA or 1.55mg/ml L-His, at pH 9.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 5mg/ml phenol, and 1mg/ml EDTA/1.55mg/ml L-His, at pH 9.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.4.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 7 mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.4.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 5mg/ml phenol, and either 4mg/ml Poloxamer 188 or 30mg/ml PEG 35000, at pH 9.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 5mg/ml phenol, and either 4mg/ml Poloxamer 188 or 30mg/ml PEG 35000, at pH 9.4.

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a formulation comprising an aqueous solution of 0.07mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0mg/ml glycerol, and 7mg/ml phenol, at pH 8.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 8.4.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 7.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 7.0.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 7.0.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 5 mg/ml phenol, at pH 7.0.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 5 mg/ml phenol, at pH 7.0.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0 mg/ml glycerol, and 7 mg/ml phenol, at pH 7.0.

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a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycylglycine, 16.0mg/ml glycerol, and 7 mg/ml phenol, at pH 7.0.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 7.0.

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a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 38.5mg/ml mannitol, and either 3mg/ml m-cresol or 1.5mg/ml phenol, at pH 7.0.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 7.8.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, and 18mg/ml benzylalcohol, at pH 7.8.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 9.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 5mg/ml phenol, and either 1mg/ml EDTA or 1.55mg/ml L-His, at pH 9.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 5mg/ml phenol, and 1mg/ml EDTA/1.55mg/ml L-His, at pH 9.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 7.4.

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a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 5mg/ml phenol, and either 4mg/ml Poloxamer 188 or 30mg/ml PEG 35000, at pH 9.4.

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a formulation comprising an aqueous solution of 0.07mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0mg/ml glycerol, and 7mg/ml phenol, at pH 7.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 7.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, and 5mg/ml phenol, at pH 7.4.

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.4.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 7 mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate , 16.0 mg/ml glycerol, 7 mg/ml phenol, and 1.55 mg/ml L-His, at pH 8.4.

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a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and either 1mg/ml EDTA or 1.55mg/ml L-His, at pH 9.4.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and either 1mg/ml EDTA or 1.55mg/ml L-His, at pH 9.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and either 4mg/ml Poloxamer 188 or 30mg/ml PEG 35000, at pH 9.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and either 4mg/ml Poloxamer 188 or 30mg/ml PEG 35000, at pH 9.4.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), glycine, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and either 4mg/ml Poloxamer 188 or 30mg/ml PEG 35000, at pH 9.4.

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a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0mg/ml glycerol, and 7mg/ml phenol, at pH 8.4.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0mg/ml glycerol, and 7mg/ml phenol, at pH 8.4.

a formulation comprising an aqueous solution of 0.05mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0mg/ml glycerol, and 7mg/ml phenol, at pH 8.4.

a formulation comprising an aqueous solution of 0.07mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 16.0mg/ml glycerol, and 7mg/ml phenol, at pH 8.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, and 5mg/ml phenol, at pH 8.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, and 5mg/ml phenol, at pH 8.4.

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a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, and 5mg/ml phenol, at pH 7.1.

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a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium

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a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 38.5mg/ml mannitol, 10 mg/ml sucrose, and either 3mg/ml m-cresol or 1.5mg/ml phenol, at pH 7.0.

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a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate/sodium dihydrogen phosphate, 17.0mg/ml mannitol, 10 mg/ml sucrose, and 18mg/ml benzylalcohol, at pH 7.8.

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a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, and 5mg/ml phenol, at pH 7.4.

a formulation comprising an aqueous solution of 0.05 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, and 5mg/ml phenol, at pH 7.4.

a formulation comprising an aqueous solution of 0.07 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, and 5mg/ml phenol, at pH 7.4.

a formulation comprising an aqueous solution of 0.01mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 7.4.

a formulation comprising an aqueous solution of 0.02mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 7.4.

a formulation comprising an aqueous solution of 0.03mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 7.4.

a formulation comprising an aqueous solution of 0.05 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 7.4.

a formulation comprising an aqueous solution of 0.07 mg/ml L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33), disodium hydrogen phosphate, 36.9mg/ml mannitol, 10 mg/ml sucrose, 5mg/ml phenol, and 1.55 mg/ml L-His, at pH 7.4.

a formulation comprising an aqueous solution, wherein the disodium hydrogen phosphate is present in a concentration of 8 mM.

In the various formulations/compositions of the invention, the GLP-2 compound can be desirably present in an amount (e.g., a volume where a particular concentration of the GLP-2 compound is predetermined) that is sufficient to detectably increase absorption of nutrients from the intestine of a significant proportion of a population of premature human infants having an impaired ability to absorb nutrients from the intestine (e.g., as determined by the outcome of preclinical testing and/or clinical trials). Thus, for example, in one aspect the invention provides a liquid pharmaceutically acceptable composition comprising a GLP-2 peptide in a concentration from about 0.001 mg/ml to about 0.5 mg/ml and in a volume sufficient to increase the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine. In another aspect, the invention provides a pharmaceutically acceptable composition comprising a GLP-2 peptide in a concentration of about 0.001-0.5 mg/ml in a volume sufficient to effectively increase nutrient absorption from the intestine of a substantial proportion of a population of infants having a condition associated with impaired nutrient absorption.

In another aspect, the invention provides method of promoting the sale and/or use of a GLP-2 compound, GLP-2 formulation, GLP-2 compound composition, or GLP-2 kit according to any of the preceding aspects, comprising distributing information related to the use of the compound in the prevention or treatment of any condition or combination of conditions recited in any of the foregoing aspects or described elsewhere herein (e.g., distributing information related to the use of a GLP-2 peptide, such as a GLP-2 peptide derivative, in increasing the absorption of nutrients in a child, such a premature human infant diagnosed as having a condition associated with impaired nutrient absorption from the intestine). The distribution of information can comprise providing sales-related information, storage-related information, administration-related information, associated treatment-related information, etc., to the public by television advertising, radio advertising, print advertising, mass mailing, billboard advertising, internet-based advertising, etc., and can include, for

example, targeted advertising to particular populations of people identified as having or being of substantial risk of developing disorders, conditions, etc., wherein the use of the various methods and compositions of the invention may be of benefit and/or to doctors, nurses, pharmacists, salespeople, medical science liaisons, health care managers, businesses, agencies, hospitals, etc., wherein such methods may be practiced and/or such compositions may be purchased. The method also can encompass holding conferences, seminars etc., and/or funding such activities with the intent of increasing the use and/or sale of such compositions (or services comprising methods provided herein).

In still another aspect, the invention provides a pharmaceutical product comprising (a) a composition according to any of the foregoing aspects or elsewhere described herein, (b) a pharmaceutically acceptable carrier, vehicle, excipient, diluent, preservative, stabilizer, flavorant, chelating agent, buffer, isotonic agent, activity-enhancing agent, solute, solubilizer, or combination of any thereof (including any multiples thereof – e.g., two diluents), or the like (such as other additives described herein) (the term "carrier", as used herein, encompasses such terms unless otherwise stated or contradicted by context), and (c) a notice associated with said container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by said agency of said pharmaceutical product for human or veterinary administration to treat at least one condition recited in any of the foregoing aspects or other condition or disease, condition, or disorder described herein.

In yet another aspect, the invention provides a composition for increasing the absorption of nutrients from the intestine of a patient and/or inducing, promoting, and/or enhancing one or more physiological responses associated with the treatment and/or prevention of a gastrointestinal related disorder comprising a means for increasing the amount of a GLP-2 compound in the patient and thereby increasing absorption of nutrients from the intestine. The means for increasing the GLP-2 compound(s) in the patient can include delivery of GLP-2 peptide-encoding nucleic acids to the patient; delivery of cells and/or vectors comprising such nucleic acids to the patient; administration of GLP-2 peptides (e.g., GLP-2, GLP-2 analogs, and/or GLP-2 derivatives) to the patient; administration of biological agents that upregulate endogenous GLP-2 expression in the host (e.g., by administration or expression of peptides that increase endogenous GLP-2 expression and/or by so-called gene activation technologies); administration of small molecule GLP-2 receptor modulators; administration of nucleic acid GLP-2 receptor modulators; and the like (as described throughout herein).

In still another aspect, the invention provides a system for increasing absorption of nutrients from the intestine of a patient (e.g., in the context of promoting the treatment of a disorder characterized as or by nutrient malabsorption) by administering a GLP-2 peptide comprising means for delivering a GLP-2 peptide to a patient under conditions that increase absorption of nutrients from the intestine in at least a significant proportion of substantially similar patients, and, optionally, means for assessing changes in nutrient absorption from the intestine in the patient. Means for delivering a GLP-2 peptide to a patient are discussed throughout herein and include, for example, administration of a GLP-2 peptide by infusion, injection, biolistic delivery ("gene gun", "protein gun", or other needle-free injection delivery), transdermal delivery, transmucosal delivery, etc., administration of a GLP-2 peptide-encoding nucleic acid by way of a plasmid, linear expression element, viral vector, or recombinant cell, and/or increasing endogenous GLP-2 expression in the patient. Means for assessing an increase in absorption of nutrients are also described herein and known in the art – e.g., evaluating the passage of unabsorbed nutrients through the digestive tract, evaluation of stool samples (these may be visually inspected for hardness, shape, smell – e.g., to determine whether these factors are indicative of steatorrhea – the patient can be monitored for explosive diarrhea, abdominal bloating, and/or excessive flatulence; but more typically fat measurements are taken as indicators of malabsorption-related conditions – a finding of more than about 6 grams of fat, for example, is often indicative of a problem), nutrient deficiencies (e.g., protein, fat, sugar, mineral, and/or vitamin deficiency – lactose, fat, and vitamin B_{12} deficiency are often useful in such contexts), blood sugar and other nutrient measurements (e.g., albumin measurements for protein deficiency), biopsy procedures (these are particularly use for detecting abnormalities in intestinal tissue), pancreatic function tests (e.g., to determine disorders caused by insufficient production of digestive enzymes in the patient), breath hydrogen testing (e.g., to assess carbohydrate absorption in infants), etc. Additional techniques related to assessing the absorption of nutrients and factors related thereto are described in, e.g., Hermann-Zaidins, J Am Diet Assoc. 1986 Sep;86(9):1171-8, 1181; Grand et al., Ciba Found Symp. 1979 Jan 16-18;(70):293-311; Chiolero et al., Crit Care Med. 2003 Mar;31(3):853-7; Langkilde et al., Eur J Clin Nutr. 1994 Nov;48(11):768-75; Strocchi et al., Can J Physiol Pharmacol. 1991 Jan;69(1):108-10; and Mobassaleh et al., Pediatrics. 1985 Jan;75(1 Pt 2):160-6.

In an additional aspect, the invention provides a composition comprising a GLP-2 compound for pharmaceutical administration comprising an amount of a GLP-2 compound sufficient to induce, promote, and/or enhance at least one physiological response associated with increasing the absorption of nutrients from the intestine and/or treating or preventing a

gastrointestinal disorder, and means for promoting the administration of the GLP-2 compound to a patient, and, optionally means for preserving the activity of the pharmaceutical compound, means for maintaining the tonicity of the compound, and/or means for maintaining the pH of the compound. Means for promoting administration of the GLP-2 compound include the various carriers, excipients, diluents, and the like, described herein and their known equivalents. Means for preserving activity (by stabilizers and preservatives), means for maintaining tonicity, and means for maintaining pH, are described elsewhere herein.

The invention also provides a method of increasing the absorption of nutrients from the intestine in a patient comprising a step for increasing the amount of GLP-2 compounds in the patient such that a detectable increase in nutrient absorption from the intestine results. The increase of GLP-2 compounds in the patient can be accomplished by the various methods described herein. For example, where the GLP-2 compound is a GLP-2 peptide a step for increasing the compound in the patient can comprise administering the peptide directly to the patient, administering a gene transfer vector comprising one or more nucleic acid sequences encoding the GLP-2 peptide, administering a nucleic acid that upregulates endogenous GLP-2 peptide expression in the host (e.g., by encoding a protein or nucleic acid that upregulates GLP-2 expression and/or by introducing nucleic acid elements that increase GLP-2 expression by endogenous gene activation techniques (e.g., in the context of methods involving the delivery of regulatory nucleic acid sequences to the cell that induce, promote, and/or enhance expression of endogenous gene sequences as discussed in, for example, US Patents 6,063,630 and 6,063,625). In a more specific aspect, the invention provides a method that also includes a step for increasing the amount of at least one additional non-GLP-2 compound factor that induces, promotes, and/or enhances the absorption of nutrients from the intestine and/or the treatment or prevention of a gastrointestinal disorder. A step for increasing the amount of such a second factor can include administration of an EGF, KGF-2, growth hormone, or other factor having such biological activity (additional examples of which are provided elsewhere herein), administering nucleic acid sequences encoding such factors, and/or upregulating endogenous expression of such factors in the patient.

The ability of the various methods of the invention of the invention to increase the absorption of nutrients is useful in the context of treating a number of diseases and/or the symptoms/outcomes thereof including short bowel syndrome, infections (bacterial, viral, and/or parasitic), celiac disease, and Crohn's disease, and may be used to ameliorate other causes of intestinal damage (e.g., damage to the intestinal lining), which, for example, may

result from the administration of intestinal-damaging drugs (e.g., neomycin and alcohol-containing compositions). Disorders that affect the remaining layers of the intestinal wall, such as blockage of the lymph vessels by lymphoma (cancer of the lymphatic system) or poor blood supply to the small intestine, also reduce absorption. Accordingly, the invention also provides a method for promoting the amelioration of negative/painful conditions and improving the quality of life in patients having such disorders. In one aspect the gastrointestinal disorder is primarily located to the lower part of the gastrointestinal tract.

In another aspect, the invention provides a method for administering a GLP-2 peptide to a premature human infant so as to increase absorption of nutrients from the intestine in the infant comprising (a) providing a lyophilized GLP-2 compound, (b) applying a step for reconstituting the lyophilized GLP-2 compound to obtain a pharmaceutically acceptable composition (preferably having a predetermined volume and concentration of GLP-2 compound), and (c) applying a step for administering the GLP-2 compound to the infant. In a somewhat related aspect, the invention provides a kit comprising a lyophilized GLP-2 compound, a means for reconstituting the GLP-2 compound, and, optionally, means for administering the GLP-2 compound (e.g., a needle or other injection device) to an infant.

In the present context the three-letter or one-letter indications of the amino acids have been used in their conventional meaning as indicated in table 1. Unless indicated explicitly, the amino acids mentioned herein are L-amino acids. Further, the left and right ends of an amino acid sequence of a peptide are, respectively, the N- and C-termini unless otherwise specified.

Table 1: Abbreviations for amino acids:

Amino acid	Tree-letter code	One-letter code
Glycine	Gly	G
Proline	Pro	P
Alanine	Ala	A
Valine	Val	V
Leucine	Leu	L
Isoleucine	Ile	I
Methionine	Met	M
Cysteine	Cys	C
Phenylalanine	Phe	F
Tyrosine	Tyr	Y
Tryptophan	Trp	W
Histidine	His	H
Lysine	Lys	K
Arginine	Arg	R
Glutamine	Gln	Q
Asparagine	Asn	N
Glutamic Acid	Glu	E
Aspartic Acid	Asp	D

Serine	Ser	S
Threonine	Thr	T

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of the invention. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing the invention in diverse forms thereof.

EXAMPLES

The following abbreviations are used:

DDE: 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl.
DIC: N,N'-diisopropylcarbodiimide.
DIEA: diisopropylethylamine.
HBTU: 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate.
HOAt: N-hydroxy-9-azabenzotriazole.
TNBS: 2,4,6 trinitro benzenesulfonic acid.
DMF: N,N-Dimethylformamide.
DCC: N,N-Dicyclohexylcarbodiimide.
NMP: N-Methyl-2-pyrrolidone.
EDPA: N-Ethyl-N,N-diisopropylamine.
EGTA: Ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid.
GTP: Guanosine 5'-triphosphate.
TFA: Trifluoroacetic acid.
THF: Tetrahydrofuran.
H-Glu(OH)-OBu^t: L-Glutamic acid α-tert-butyl ester.
Cap-ONSu: Octanoic acid 2,5-dioxopyrrolidin-1-yl ester.
Lau-ONSu: Dodecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
Myr-ONSu: Tetradecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
Pal-ONSu: Hexadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
Ste-ONSu: Octadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
HPLC: High Performance Liquid Chromatography.
amu: atomic mass units.

Lit-Glu(ONSu)-OBu^t: N$^\alpha$-Lithochoyl-L-glutamic acid α-t-butyl ester γ-2,5-dioxopyrrolidin-1-yl ester.

Cap-Glu(ONSu)-OBu^t: N$^\alpha$-Octanoyl-L-glutamic acid α-t-butyl ester γ-2,5-dioxopyrrolidin-1-yl ester.

Cac-Glu(ONSu)-OBu^t: N$^\alpha$-Decanoyl-L-glutamic acid α-t-butyl ester γ-2,5-dioxopyrrolidin-1-yl ester.

Lau-Glu(ONSu)-OBu^t: N$^\alpha$-Dodecanoyl-L-glutamic acid α-t-butyl ester γ-2,5-dioxopyrrolidin-1-yl ester.

Myr-Glu(ONSu)-OBu^t: N$^\alpha$-Tetradecanoyl-L-glutamic acid α-t-butyl ester γ-2,5-dioxopyrrolidin-1-yl ester.

Pal-Glu(ONSu)-OBu^t : N$^\alpha$-Hexadecanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester.

Ste-Glu(ONSu)-OBu^t : N$^\alpha$-Octadecanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester.

Lau-β-Ala-ONSu: N$^\beta$-Dodecanoyl-β-alanine 2,5-dioxopyrrolidin-1-yl ester.

Myr-β-Ala- ONSu: N$^\beta$- Tetradecanoyl-β-alanine 2,5-dioxopyrrolidin-1-yl ester

Pal-β-Ala-ONSu: N$^\beta$-Hexadecanoyl-β-alanine 2,5-dioxopyrrolidin-1-yl ester.

Lau-GABA-ONSu: N$^\gamma$-Dodecanoyl-γ-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester.

Myr-GABA-ONSu: N$^\gamma$-Tetradecanoyl-γ-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester.

Pal-GABA-ONSu: N$^\gamma$-Hexadecanoyl-γ-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester .

Ste-GABA-ONSu: N$^\gamma$-Octadecanoyl-γ-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester.

Pal-Isonip-ONSu: N-Hexadecanoyl-piperidine-4-carboxylic acid 2,5-dioxopyrrolidin-1-yl ester.

Pal-Glu(OBu^t)-ONSu: N$^\alpha$-Hexadecanoyl-L-glutamic acid α-2,5-dioxopyrrolidin-1-yl ester γ-t-butyl ester.

HOOC-$(CH_2)_6$-COONSu: ω–Carboxyheptanoic acid 2,5-dioxopyrrolidin-1-yl ester.

HOOC-$(CH_2)_{10}$-COONSu: ω–Carboxyundecanoic acid 2,5-dioxopyrrolidin-1-yl ester.

HOOC-$(CH_2)_{12}$-COONSu: ω–Carboxytridecanoic acid 2,5-dioxopyrrolidin-1-yl ester.

HOOC-$(CH_2)_{14}$-COONSu: ω–Carboxypentadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.

HOOC-$(CH_2)_{16}$-COONSu: ω–Carboxyheptadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.

HOOC-$(CH_2)_{18}$-COONSu: ω–Carboxynonadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.

Example 1

Preparation of derivatives of GLP-2 peptide analogs by peptide synthesis.

The acylation is done on the fully protected resin-bound peptide where only the ε-amino group to be acylated has been deprotected. The appropriately protected resin bound peptide is synthesized using Fmoc chemistry, e.g.:

↓ Boc-[1-33,Lys(Dde)]-Resin
↓ 2%Hydrazine/DMF treatment to remove the Dde group.
↓ Acylation with Fmoc-Glu(γ-OH)-OBu^t via HOAt / DIC / DIEA / NMP.
↓ Piperidine treatment to remove the Fmoc group.
↓ Acylate with C16 acid via HOAt / DIC / DIEA / NMP.
↓ TFA deprotection.
↓ HPLC-Purification
↓ Lyophilization
↓ Analysis by LC-MS and analytical HPLC.

The spacer and fatty acid chain length may then be varied. Keeping the acylation position fixed, three spacers: γ-Glutamic acid, γ-aminobutyric acid, β-Alanine and no spacer, and three fatty acids (C12, C14 and C16) as well as cholic, lithocholic, and pentylbenzoic acids were tested.

Synthesis of protected peptidyl resin:

Protected amino acid derivatives used:
Fmoc-Ala-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OBut)-OH, Boc-His(Boc)-OH, Fmoc-His(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OBut)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Lys(Dde)-OH, Boc-Lys(Fmoc)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Ser(But)-OH, Fmoc-Thr(But)-OH, Fmoc-Trp(Boc)-OH

Synthesis of N$^{\alpha}$-hexadecanoyl-Glu(ONSu)-OBu^t.

To a suspension of H-Glu(OH)-OBu^t (4.2 g, 20.6 mmol), DMF (500 ml) and EDPA (2.65 g, 20.6 mmol) was added drop by drop a solution of Pal-ONSu (7.3 g, 20.6 mmol) in DMF (100

ml). The reaction mixture was stirred for 64 h at room temperature and then concentrated *in vacuo* to a total volume of 20 ml. The residue was partitioned between 10% aqueous citric acid (300 ml) and ethyl acetate (250 ml), and the phases were separated. The organic phase was concentrated *in vacuo* and the residue dissolved in DMF (50 ml). The resulting solution was added drop by drop to a 10% aqueous solution of citric acid (500 ml) kept at 0 °C. The precipitated compound was collected and washed with iced water and dried in a vacuum drying oven. The dried compound was dissolved in DMF (45 ml) and HONSu (2.15 g, 18.7 mmol) was added. To the resulting mixture was added a solution of N,N'-dicyclohexylcarbodiimide (3.5 g, 17 mmol) in dichloromethane (67 ml). The reaction mixture was stirred for 16 h at room temperature, and the precipitated compound was filtered off. The precipitate was recrystallised from n-heptane/2-propanol to give the title compound (6.6 g, 72%).

Example 2

Synthesis of D3E/L17K((*S*)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33).

2.a Synthesis of the protected peptidyl resin:

The protected peptidyl resin was synthesized according to the Fmoc strategy on an Applied Biosystems 431A peptide synthesizer in 0.25 mmol scale using the manufacturer supplied FastMoc UV protocols which employ HBTU (2-(1H-Benzotriazol-1-yl-)-1,1,3,3 tetramethyluronium hexafluorophosphate) mediated couplings in NMP (N-methyl pyrrolidone), and UV monitoring of the deprotection of the Fmoc protection group. The starting resin (400mg) used for the synthesis was (4-((2', 4'-dimethoxyphenyl)-(Fmoc-Glu(OBut)-O-p-Benzyloxybenzyl resin (Wang resin) (Novabiochem, Bad Soden, Germany. cat. #: 04-12-2052) with a substitution capacity of 0.53 mmol / g.

The protected aminoacid derivatives used were Fmoc-Ala-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OBut)-OH, Boc-His(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OBut)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(DDE)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Ser(But)-OH, Fmoc-Thr(But)-OH, Fmoc-Trp(Boc)-OH.

The yield was 870mg peptidyl resin.

2.b *Dde removal and acylation*

To the protected peptidyl resin resulting from (1.a) (290mg, 72µmol) is added NMP (N-Methyl pyrrolidon)(2ml), and a freshly prepared solution of hydrazine hydrate 2% in NMP (10ml). The reaction mixture is stirred for 3min at room temperature, and then filtered (glas filter).

More hydrazine solution (22ml) is added on the filter, the hydrazine is left to react for 15mn on the filter, and then filtered off by applying vacuum.

The resin is then washed extensively with NMP, dichloromethane and NMP.

To the Dde deprotected resin in NMP (≈ 5ml), is added N-C_{16}-Glu-α-OtBu-γ-ONSu (N^{α}-hexadecanoyl-L-glutamic acid α-tert-butyl ester γ-succinimidyl ester) (4eq), and DIEA (diisopropylethylamine)(4 eq). The reaction mixture is stirred for 1h at room temperature. Then more N-C_{16}-Glu-α-OtBu-γ-ONSu (4eq) is added, together with DIEA (4 eq). The reaction mixture is stirred overnight at room temperature. The reaction mixture is filtered and the resin is washed extensively with NMP, dichloromethane, 2-propanol, methanol and diethyl ether.

2.c Cleavage of the acylated peptide from the resin:

The peptide is cleaved from the protected peptidyl resin by stirring with a mixture of TFA (trifluoro acetic acid) (2 ml), triisopropylsilane (50 µl) and water (50 µl) for 60 min at room temperature. The cleavage mixture is filtered and the filtrate is concentrated to approximately 1 ml by a stream of nitrogen. The crude peptide is precipitated from this oil with diethyl ether (49.5 ml), washed 3 times with diethyl ether (3 times 50 ml) and dried to a white powder.

2.d Purification of the peptide:

The crude peptide is dissolved in water/acetonitrile (65:35) (100ml) adjusted to pH 7.5 with NH_4OH and purified by semipreparative HPLC on a 25 mm x 250 mm column packed with 7µ C-18 silica. The column is eluted with a gradient of 50 to 70% acetonitrile against 0.1% TFA/water at 10 ml/min at a temperature of 40 °C for 47mn. The peptide containing fractions are collected, diluted with 3 volumes of water and lyophilized.

The final product obtained is characterized by RP-HPLC / ion spray mass spectrometry (LC-MS) (retention time and molecular mass) and by analytical RP-HPLC (retention time and peptide amount). The peptide amount is calculated by comparing the UV detector response with that of a GLP-2 standard where the amount had been determined by amino acid analysis.The RP-HPLC analysis is performed on a Vydac 218TP54 4.6mm x 250mm 5µ C-18 silica column (The Separations Group, Hesperia) with UV detection at 214 nm . The column is equilibrated with 0.1% TFA / H_2O and eluted by a gradient of 0 to 90% CH_3CN against 0.1%TFA/water for 50 min at 42 °C, wi.th a flow of 0.5ml/mn. The retention time is found to be 35.8min, and the peptide yield to be 29.3mg.

The LC-MS analysis is performed using a Symmetry 3.0 mm x 150 mm 5µ C-18 silica column (Waters, Milford MA., USA) which is eluted at 1 ml/min at room temperature. It is equilibrated with 5 % CH_3CN / 0.1% TFA / H_2O and eluted by a gradient of 5% CH_3CN / 0.1%

TFA / H_2O to 90% CH_3CN / 0.1% TFA / H_2O during 15 min. Besides the UV detection at 214nm, a fraction of the column eluate is introduced into the ionspray interface of a PE-Sciex API 100 mass spectrometer. The mass range 300 - 3000 amu is scanned every 2 seconds during the run.

Using these conditions, the retention time of the product as determined from the UV trace is found to be 6.1min, and the molecular mass is found to be 4204.4 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 3

Synthesis of D3E/K30R/D33E/34K((*S*)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33) (Lys residue added in C-terminal).

The starting resin used for the synthesis was Fmoc-Lys(Dde)-2Cl-Trityl resin, prepared from Fmoc-Lys(Dde)-OH and 2-Cl-Trityl chloride resin (Novabiochem, Bad Soden, Germany. cat. #: 01-64-0114) after the procedure described by the manufacturer (substitution capacity of 1.13 mmol/g).

The protected peptidyl resin (200mg, 85µmol) was synthesized according to the Fmoc strategy as in example (2.a), Dde deprotected and acylated with N-C_{16}-Glu-α-OtBu-γ-ONSu (N^{α}-hexadecanoyl-L-glutamic acid α-tert-butyl ester γ-succinimidyl ester) as described in (2.b). Cleavage from the resin and purification were done according to (2.c and 2.d).

The retention time obtained under the elution conditions described in (2.d) was 36.7min, and the peptide yield was 1.3mg.

By LC-MS analysis of the product, a retention time of 6.6min was found from the UV trace, and the molecular mass was found to be 4319.4 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 4

Synthesis of D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33).

The protected peptidyl resin (200mg, 21µmol) was synthesized according to the Fmoc strategy as in example (2.a), Dde deprotected and acylated with C_{16}-GABA-ONSu (N-hexadecanoyl-γ-amino-butyric acid succinimidyl ester) as described in (2.b) for acylation with N-C_{16}-Glu-α-OtBu-γ-ONSu. Cleavage from the resin and purification were done according to (2.c and 2.d).

Cleavage from the resin and purification were done according to example (2.c) and (2.d).

The retention time obtained under the elution conditions described in (2.d) was 36.5min, and the peptide yield was 1.9mg.

By LC-MS analysis of the product, a retention time of 4.9min was found from the UV trace, and the molecular mass was found to be 4161.0 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 5

Synthesis of D3E/L17K(3-(hexadecanoylamino)propionyl)K30R/D33E-GLP-2(1-33).

The protected peptidyl resin (200mg, 21µmol) was synthesized according to the Fmoc strategy as in example (2.a), Dde deprotected and acylated with C_{16}-oyl-β-Ala-ONSu (N-hexadecanoyl-β-alanine-succinimidyl ester) as described in (2.b) for acylation with N-C_{16}-Glu-α-OtBu-γ-ONSu. Cleavage from the resin and purification were done according to (2.c and 2.d).

Cleavage from the resin and purification were done according to (2.c and 2.d).

The retention time obtained under the elution conditions described in (2.d) was 36.0min, and the peptide yield was 2.8mg.

By LC-MS analysis of the product, a retention time of 4.7min was found from the UV trace, and the molecular mass was found to be 4146.6 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 6

Synthesis of D3E/L17K(hexadecanoyl)/K30R/D33E-GLP-2(1-33).

The protected peptidyl resin (200mg, 21µmol) was synthesized according to the Fmoc strategy as in example (2.a), Dde deprotected and acylated with C_{16}-oyl-ONSu (hexadecanoic acid succinimidyl ester) as described in (2.b) for acylation with N-C_{16}-Glu-α-OtBu-γ-ONSu.

Cleavage from the resin and purification were done according to (2.c and 2.d).

The retention time obtained under the elution conditions described in (2.d) was 36.9min, and the peptide yield was 2.6mg.

By LC-MS analysis of the product, a retention time of 5.1min was found from the UV trace, and the molecular mass was found to be 4076.4 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 7

Synthesis of D3E/L17K(choloyl)/K30R/D33E-GLP-2(1-33).

The protected peptidyl resin (250mg, 27µmol) was synthesized as in example (2.a). The Dde protective group is removed as in example (2.b).

To a mixture of cholic acid (817mg), HOAt (N-hydroxy-9-azabenzotriazole) (135mg) and DIC (N,N'-diisopropylcarbodiimide) (155µl) is added a mixture of NMP and dichloromethane (1:1 v/v) (4ml). The reaction mixture is stirred at ambient temperature for 15min. The peptidyl resin is then added, together with DIEA (diisopropylethylamine) (170µl). The reaction mixture is stirred overnight at ambient temperature. The resin is then filtered, washed thoroughly with NMP, and then with dichloromethane, 2-propanol, methanol and diethylether. Cleavage from the resin and purification were done according to (2.c and 2.d).
The retention time obtained under the elution conditions described in (2.d) was 30.0min, and the peptide yield was 2.2mg.
By LC-MS analysis of the product, a retention time of 4.2min was found from the UV trace, and the molecular mass was found to be 4228.2 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 8

Synthesis of 1H((*S*)-4-carboxy-4-(hexadecanoylamino)butanoyl)/D3E/K30R/D33E-GLP-2(1-33).

8.a Synthesis of the protected peptidyl resin:

The protected peptidyl resin was synthesized according to the Fmoc strategy on an Applied Biosystems 431A peptide synthesizer in 0.25 mmol scale using the manufacturer supplied FastMoc UV protocols which employ HBTU (2-(1H-Benzotriazol-1-yl-)-1,1,3,3 tetramethyluronium hexafluorophosphate) mediated couplings in NMP (N-methyl pyrrolidone), and UV monitoring of the deprotection of the Fmoc protection group. The starting resin (454mg, 0.25mmoles) used for the synthesis was (4-((2', 4'-dimethoxyphenyl)-(Fmoc-Glu(OBut)-O-p-Benzyloxybenzyl resin (Wang resin) (Novabiochem, Bad Soden, Germany. cat. #: 04-12-2052) with a substitution capacity of 0.55 mmol / g.
The protected aminoacid derivatives used were Fmoc-Ala-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OBut)-OH, Fmoc-His(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OBut)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Ser(But)-OH, Fmoc-Thr(But)-OH, Fmoc-Trp(Boc)-OH.
The yield was 1707mg peptidyl resin.

8.b Acylation

To the peptidyl resin (200mg, 29µmoles) in NMP (≈ 5ml), is added N-C_{16}-Glu-α-OtBu-γ-ONSu (N^{α}-hexadecanoyl-L-glutamic acid α-tert-butyl ester γ-succinimidyl ester) (4eq), and DIEA (diisopropylethylamine)(4 eq). The reaction mixture is stirred for 1h at room temperature.
Then more N-C_{16}-Glu-α-OtBu-γ-ONSu (4eq) is added, together with DIEA (4 eq). The

reaction mixture is stirred overnight at room temperature. The reaction mixture is filtered and the resin is washed extensively with NMP, dichloromethane, 2-propanol, methanol and diethyl ether.

Cleavage from the resin and purification were done according to (2.c and 2.d).

The retention time obtained under the elution conditions described in (2.d) was 37.0min, and the peptide yield was 6.0mg.

By LC-MS analysis of the product, a retention time of 6.5min was found from the UV trace, and the molecular mass was found to be 4189.8 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 9

Synthesis of H1K-N$^{\varepsilon}$-((*S*)-4-carboxy-4-(hexadecanoylamino)butanoyl)/D3E/K30R/D33E-GLP-2(1-33).

9.a Synthesis of the protected peptidyl resin:

The protected peptidyl resin was synthesized according to the Fmoc strategy on an Applied Biosystems 431A peptide synthesizer in 0.25 mmol scale using the manufacturer supplied FastMoc UV protocols which employ HBTU (2-(1H-Benzotriazol-1-yl-)-1,1,3,3 tetramethyluronium hexafluorophosphate) mediated couplings in NMP (N-methyl pyrrolidone), and UV monitoring of the deprotection of the Fmoc protection group. The starting resin (434mg, 0.24mmoles) used for the synthesis was (4-((2', 4'-dimethoxyphenyl)-(Fmoc-Glu(OBut)-O-p-Benzyloxybenzyl resin (Wang resin) (Novabiochem, Bad Soden, Germany. cat. #: 04-12-2052) with a substitution capacity of 0.55 mmol / g.

The protected aminoacid derivatives used were Fmoc-Ala-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OBut)-OH, Fmoc-His(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OBut)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Boc-Lys(Fmoc)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Ser(But)-OH, Fmoc-Thr(But)-OH, Fmoc-Trp(Boc)-OH.

The yield was 1551mg peptidyl resin.

9.b Acylation

To the peptidyl resin (200mg, 31µmoles) in NMP (≈ 5ml), is added N-C_{16}-Glu-α-OtBu-γ-ONSu (N$^{\alpha}$-hexadecanoyl-L-glutamic acid α-tert-butyl ester γ-succinimidyl ester) (4eq), and DIEA (diisopropylethylamine)(4 eq). The reaction mixture is stirred for 1h at room temperature. Then more N-C_{16}-Glu-α-OtBu-γ-ONSu (4eq) is added, together with DIEA (4 eq). The reaction mixture is stirred overnight at room temperature. The reaction mixture is filtered and the resin is washed extensively with NMP, dichloromethane, 2-propanol, methanol and diethyl ether.

Cleavage from the resin and purification were done according to (2.c and 2.d).
The retention time obtained under the elution conditions described in (2.d) was 36.8min, and the peptide yield was 4.4mg.
By LC-MS analysis of the product, a retention time of 6.4min was found from the UV trace, and the molecular mass was found to be 4180.2 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 10

Synthesis of H1K-N$^{\alpha}$-((*S*)-4-carboxy-4-(*hexadecanoylamino*)butanoyl)/D3E/K30R/D33E-GLP-2(1-33).

10.a Synthesis of the protected peptidyl resin:
The protected peptidyl resin was synthesized according to the Fmoc strategy on an Applied Biosystems 431A peptide synthesizer in 0.25 mmol scale using the manufacturer supplied FastMoc UV protocols which employ HBTU (2-(1H-Benzotriazol-1-yl-)-1,1,3,3 tetramethyluronium hexafluorophosphate) mediated couplings in NMP (N-methyl pyrrolidone), and UV monitoring of the deprotection of the Fmoc protection group. The starting resin (455mg, 0.25mmoles) used for the synthesis was (4-((2', 4'-dimethoxyphenyl)-(Fmoc-Glu(OBut)-O-p-Benzyloxybenzyl resin (Wang resin) (Novabiochem, Bad Soden, Germany. cat. #: 04-12-2052) with a substitution capacity of 0.55 mmol / g.
The protected aminoacid derivatives used were Fmoc-Ala-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OBut)-OH, Fmoc-His(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OBut)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Dde)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Ser(But)-OH, Fmoc-Thr(But)-OH, Fmoc-Trp(Boc)-OH.
The yield was 1167mg peptidyl resin.

10.b Acylation
To the peptidyl resin (200mg, 43µmoles) in NMP (≈ 5ml), is added N-C_{16}-Glu-α-OtBu-γ-ONSu (N$^{\alpha}$-hexadecanoyl-L-glutamic acid α-tert-butyl ester γ-succinimidyl ester) (4eq), and DIEA (diisopropylethylamine)(4 eq). The reaction mixture is stirred for 1h at room temperature. Then more N-C_{16}-Glu-α-OtBu-γ-ONSu (4eq) is added, together with DIEA (4 eq). The reaction mixture is stirred overnight at room temperature. The reaction mixture is filtered and the resin is washed extensively with NMP, dichloromethane, 2-propanol, methanol and diethyl ether.
The Dde protective group is then removed as in (2.b).
Cleavage from the resin and purification were done according to (2.c and 2.d).

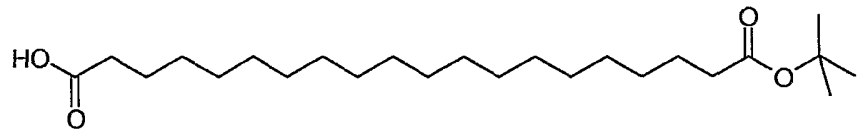
The retention time obtained under the elution conditions described in (2.d) was 37.0min, and the peptide yield was 4.0mg.
By LC-MS analysis of the product, a retention time of 6.5min was found from the UV trace, and the molecular mass was found to be 4180.2 amu, which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

The characterisation includes retention time in an analytical RP-HPLC system, retention time in an LC-MS system and a molecular weight determination in the LC-MS system. The total amount of peptide synthesised were calculated by comparison of peak areas with those from a GLP-2 standard.

Example 11

Building block synthesis:

Building block 1 Eicosanedioic acid mono-tert-butyl ester:



To eicosanedioic acid (3 g, 8.76 mmol) was added toluene (25 mL) and N,N dimethylformamide di-*tert*-butylacetal (2.1 mL, 8.76 mmol). The mixture is heated to 95°C for 30 minutes, the mixtures is filtered and evaporated to an oil, which is redisolved in dichloromethane and washed with water. The organic phase is dried and evaporated to give 722 mg (21 %) of the title compound, which was subsequently used without any further purification.
^{1}H NMR ($CDCl_3$): δ10.90 (br s, 1H), 2.35 (t, 2H), 20 (t, 2H), 1.60 (m, 4H), 1.45 (s, 9H); 1.40-1.20 (m, 28H)

Synthesis of L17K(3-(ω-caboxypentadecanoylamino)propionyl)K30R/D33E-GLP-2(1-33)

59.a Synthesis of the protected peptidyl resin:

The protected peptidyl resin was synthesized according to the Fmoc strategy on an Applied Biosystems 431A peptide synthesizer in 0.25 mmol scale using the manufacturer supplied FastMoc UV protocols which employ HBTU (2-(1H-Benzotriazol-1-yl-)-1,1,3,3 tetramethyluronium hexafluorophosphate) or HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) mediated couplings in NMP (N-methyl

pyrrolidone), and UV monitoring of the deprotection of the Fmoc protection group. The starting resin (400mg) used for the synthesis was (4-((2', 4'-dimethoxyphenyl)-(Fmoc-Glu(OBut)-O-p-Benzyloxybenzyl resin (Wang resin) (Novabiochem, Bad Soden, Germany. cat. #: 04-12-2052) with a substitution capacity of 0.53 mmol / g.

The protected aminoacid derivatives used were Fmoc-Ala-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OBut)-OH, Boc-His(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OBut)-OH, Fmoc-(FmocHmb)Gly-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(DDE)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Ser(But)-OH, Fmoc-Thr(But)-OH, Fmoc-Trp(Boc)-OH.

59.b *Dde removal and acylation*

To the protected peptidyl resin resulting from (59.a) (300 mg, 75µmol) is added a freshly prepared solution of hydrazine hydrate 2% in NMP (12ml). The reaction mixture is shaken for 3 minuntes at room temperature, and then filtered. More hydrazine solution (20ml) is added on the reaction mixture is shaken for 15 minutes and then filtered. The resin is then washed extensively with NMP (5 x 20 mL).

Fmoc-beta-alanine (93 mg, 0.30 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (49 mg, 0.30 mmol) and diisopropylethylamine (13 µL, 0.075 mmol) was dissolved in NMP (20 mL) and added to the Dde deprotected resin, *N,N'*-diisopropylcarbodiimide (46 µL, 0.3 mmol) was added and the mixture was shaken overnight. The resin was filtered and washed with NMP (5 x 20 mL). The resin was treated with piperidine (20 % in NMP, 20 mL) for 10 minutes followed by another treatment of piperidine (20 % in NMP, 20 mL) for 10 minutes. The resin was filtered and washed with NMP. (5 x 20 mL).

Hexadecanedioic acid mono-(2,5-dioxopyrrolidin-1-yl) ester (Ebashi *et al.* EP511600) (107 mg, 0.3 mmol) was dissolved in NMP (20 mL), added to the resin and shaken overnight at room temperature. The reaction mixture is filtered and the resin is washed extensively with NMP, dichloromethane, 2-propanol, methanol and diethyl ether.

2.c Cleavage of the acylated peptide from the resin:

The peptide is cleaved from the protected peptidyl resin by stirring with a mixture of TFA (trifluoro acetic acid) (20 ml), triisopropylsilane (500 µl) and water (500 µl) for 60 min at room temperature. The cleavage mixture is filtered and the filtrate is concentrated to approximately 2 ml by a stream of nitrogen. The crude peptide is precipitated from this oil with diethyl ether (10 ml), washed 3 times with diethyl ether (3 times 10 ml) and dried to a white powder.

2.d Purification of the peptide:

The crude peptide is dissolved in water/acetonitrile (65:35) adjusted to pH 7.5 with NH_4OH and purified by preparative HPLC (Waters, Prep LC2000) on a 25 mm x 250 mm column packed with C-18 silica. The column is eluted with a gradient of 43 to 60% acetonitrile

against 0.1% TFA/water at 10 ml/min at room temperature for 40minutes. The peptide containing fractions are collected, diluted with 3 volumes of water and lyophilized, yield determined by dry weight 21 mg.

The final product obtained is characterized by RP-HPLC / ion spray mass spectrometry (LC-MS) (retention time and molecular mass)

The LC-MS analysis is performed using a Symmetry 3.0 mm x 150 mm 5µ C-18 silica column (Waters, Milford MA., USA) which is eluted at 1 ml/min at room temperature. It is equilibrated with 5 % CH_3CN / 0.1% TFA / H_2O and eluted by a gradient of 5% CH_3CN / 0.1% TFA / H_2O to 90% CH_3CN / 0.1% TFA / H_2O during 10 min. Besides the UV detection at 214nm, a fraction of the column eluate is introduced into the ionspray interface of a PE-Sciex API 100 mass spectrometer. The mass range 300 - 2000 amu is scanned every 2 seconds during the run.

Using these conditions, the retention time of the product as determined from the UV trace is found to be 3.84 min, and the molecular masspeaks identified were 1042.1 (m/4) and 1388.6 (m/3) which is in agreement with the expected structure within the experimental error of the method (± 1 amu).

Example 12

Synthesis of L17K(3-(ω-caboxynonadecanoylamino)propionyl)K30R/D33E-GLP-2(1-33)

The protected peptidyl resin (100mg, 25µmol) was synthesized according to the Fmoc strategy as in example (59.a), Dde deprotected and acylated with Fmoc-beta-alanine followed by removal of the Fmoc group was done as described in 59.b. The acylation with eicosanedioic acid mono-tert-butyl ester was done as follows. Eicosanedioic acid mono-tert-butyl ester (40 mg, 0.1 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (16 mg, 0.1 mmol) and diisopropylethylamine (4 µL, 0.025 mmol) was dissolved in NMP (2 mL) and added to the Fmoc deprotected resin, *N,N'*-diisopropylcarbodiimide (15 µL, 0.1 mmol) was added and the mixture was shaken overnight.

Cleavage from the resin and purification were done according to (59.c and 59.d).

The final product obtained is characterized by RP-HPLC / ion spray mass spectrometry (LC-MS) (retention time and molecular mass) and by analytical RP-HPLC (retention time and peptide amount). The peptide amount is calculated by comparing the UV detector response with that of a GLP-2 standard where the amount had been determined by amino acid analysis.The RP-HPLC analysis is performed on a Vydac 218TP54 4.6mm x 250mm 5µ C-18 silica column (The Separations Group, Hesperia) with UV detection at 214 nm . The column

is equilibrated with 0.1% TFA / H_2O and eluted by a gradient of 0 to 90% CH_3CN against 0.1%TFA/water for 50 min at 42 °C, wi.th a flow of 0.5ml/mn. The retention time is found to be 35.0 min, and the peptide yield to be 100 µg.

By LC-MS analysis of the product was done at the same conditions as described in 59.d, a retention time of 4.25 min was found from the UV trace, and the molecular masspeaks identified were 1055.1 (m/4) and 1407.6 (m/3) which is in agreement with the expected structure

Example 13

Preparation of GLP-2 peptide analogs by recombinant technology in yeast.

The yeast expression system

The host strain, which has been used to express GLP-2 precursors is a polyploid strain designated ME1719. ME1719 has phenotypes which lack two aspartyl proteases, i.e., (1) yapsin 1 (previously called YAP3p) which cleaves C-terminal side of mono- or dibasic amino acid residues (Egel-Mitani, M, Flygenring, H.A. & Hansen, M.T., YEAST 6:127-137, 1990) and (2) vacuolar protease A (Pra1p) responsible for activation of other proteases such as protease B, carboxypeptidase Y, aminopeptidase I, RNase, alkaline phosphatase, acid trehalase and exopolyphosphatase. ME1719 can stably produce small peptides in high yield, which contain mono- or dibasic amino acids. Among other peptides, such as glucagon and GLP-1, GLP-2 is the most advantageous to use this yeast strain (Egel-Mitani,, M., Brandt , J. and Vad, K.: Method for the production of polypeptides is described in US Patent US 6,110,703, 29.08.2000 and Egel-Mitani, M., Anderson, A.S., Diers, I, Hach, M., Thim, L., Hastrup, S. and Vad, K.: Enzyme and Microbial Technology 26:671-677, 2000). Moreover, the triosephosphate isomerase gene (TPI1) has been disrupted in this strain, which phenotype makes it possible to utilise glucose as a selection marker of yeast transformants, which enable to obtain high biomass, hitherto high yield in continuous fermentation.

In order to express human GLP-2 in yeast, S. cerevisiae, in which human amino acid sequence has been obtained from EMBL (V01515 HSGLUC), yeast codon usage has been introduced to optimize GLP-2 production. In the present example data for four GLP-2 peptide analog expression plasmids are included; 1) A2G-GLP-2(1-33), 2) M10K/K30R-GLP-2(1-33), 3) M10L/L17K/K30R-GLP-2(1-33), 4) L17K/K30R-GLP-2(1-33).

DNA and amino acid mutations were made according to the wild-type human amino acid sequence (HADGSFSDEMNTILDNLAARDFINWLIQTKITD) with corresponding yeast

codon usage. DNA sequence of the GLP-2 peptide analogs was inserted in an expression vector (Fig. 7). As shown in Fig.7 the GLP-2 expression is driven by TPI promoter and MFα signal-leader sequence followed by the GLP-2 coding sequence inserted between NcoI and XbaI restriction enzyme sites. Procedures for preparing a DNA construct using polymerase chain reaction using specific primers are well known to persons skilled in the art (cf. PCR Protocols, 1990, Academic Press, San Diego, California, USA) and may be used for the preparation of any GLP-2 peptide analog according to the invention.

Fermentation and determination of yields

For small-scale batch cultures, transformants were inoculated in 5 ml of YPD + Ca^{2+} medium (1% yeast extract, 2% peptone, 5mM $CaCl_2$) and cultivated with shaking (200rpm) at 30°C for 3 days. Culture supernatant were analysed by HPLC after cells had been spun down by centrifugation. The following HLPC method was used:

Column:	C4 Jupiter,300Å, 5um, 4,6x250mm
Buffer A:	0.10% TFA
Buffer B:	0.07% TFA in CH_3CN
Flow:	1ml/min
Gradient:	30-60%B over 15 min. at room temperature.

The following yields of GLP-2 peptide analogs were obtained in small-scale (5 ml) cultures in the ME1729 host strain:

Construct	Plasmid	Yeast transformant	Yield
A2G-GLP-2(1-33)	pKV220	YES2651	13.0 mg/L
M10K/K30R-GLP-2(1-33)	pME2794	YES2795	32.8 mg/L
M10L/L17K/K30R-GLP-2(1-33)	pME2765	YES2766	36.6 mg/L
L17K/K30R-GLP-2(1-33)	pME2735	YES2736	33.9 mg/L

Purification and characterisation

All GLP-2 peptide analogs according to the present invention may be purified using the following overall purification scheme:

No	Step	Overall Yield

1	Fermentation liquid	100%
	▼	
2	Capture Column	75%
	▼	
3	Precipitation	71%
	▼	
4	Hydroxyapatite Column	60%
	▼	
5	Source30Q Column	53%
	▼	
6	RP-HPLC Column	45%
	▼	
7	Precipitation	43%

The purified peptides were analysed by amino acid sequence analysis and mass spectrometry. N-terminal amino acid sequences were determined by automated Edman degradations using an Applied Biosystem Model 494 Protein Sequencer essentially as described by the manufacturer. By using an optimised system it was possible to determine the partial sequence of as little as 300-500 fmol of peptide.

Mass spectrometric analysis was performed on a Voyager RP MALDI-TOF instrument (Perseptive Biosystems Inc., Framingham, MA) equipped with a nitrogen laser (337 nm). The instrument was operated in linear mode with delayed extraction, and the accelerating voltage in the ion source was 25kV.

Sample preparation was done as follows: 1 µl sample-solution was mixed with 1 µl matrix-solution (alpha-cyano-4-hydroxy-cinnamic acid dissolved in a 5:4:1 (v/v/v) mixture of acetonitrile:water:3%(v/v) TFA) and 1 µl was deposited on the sample plate and allowed to dry. Calibration was performed using external standards and the accuracy of the mass determinations was within 0.1%.

Peptide	Found MW	Calculated MW
Native GLP-2	3767	3766.2
A2G-GLP-2(1-33)	3751	3752.1
M10K/K30R-GLP-2(1-33)	3793	3805.2
M10L/L17K/K30R-GLP-2(1-33)	3793	3791.2
L17K/K30R-GLP-2(1-33)	3809	3809.2

Preparation of GLP-2 derivatives from GLP-2 peptides prepared by recombinant technology in yeast.

The following general procedure was used for the acylation of GLP-2 peptides prepared by recombinant technology in yeast:

50 mg of lyophilized peptide was dissolved in 3.2 ml of water at 4°C. The pH was adjusted to 12.2 with 1 M of NaOH. The solution was allowed to stand for 2 min at 10°C and the pH was adjusted to 9.5 with 1M HAc. 7 ml of 4°C cold N-Methyl-2-pyrrolidone (NMP) was added and the temperature adjusted to 10°C. The pH was adjusted to 11.5 with triethylamine. The acylation reagent (e.g. Pal-β-Ala-ONSu) was dissolved in NMP to a concentration of 20 mg/ml. A volume of 0.78 ml of this solution was added to the peptide solution and the acylation reaction was allowed to continue for 15 min at 15°C under stirring. The reaction was stopped by the addition of 0.65 ml of a 100 mg/ml glycine solution and the pH was adjusted to 8.5 with 5M of HAc. The acylated GLP-2 peptide analog was purified by RP-HPLC. Examples of different acylation reagents that may be used according to this example includes but are not limited to:

Lau-Glu(ONSu)-OBu^t: N$^\alpha$-Dodecanoyl-L-glutamic acid α-t-butyl ester γ-2,5-dioxopyrrolidin-1-yl ester.

Pal-Glu(ONSu)-OBu^t : N$^\alpha$-Hexadecanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester.

Lau-β-Ala-ONSu: N$^\beta$-Dodecanoyl-β-alanine 2,5-dioxopyrrolidin-1-yl ester.

Myr-β-Ala- ONSu: N$^\beta$- Tetradecanoyl-β-alanine 2,5-dioxopyrrolidin-1-yl ester.

Pal-β-Ala-ONSu: N$^\beta$-Hexadecanoyl-β-alanine 2,5-dioxopyrrolidin-1-yl ester.

Lau-GABA-ONSu: N$^\gamma$-Dodecanoyl-γ-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester.

Myr-GABA-ONSu: N$^\gamma$-Tetradecanoyl-γ-aminobutyricacid 2,5-dioxopyrrolidin-1-yl ester.

Pal-GABA-ONSu: N$^\gamma$-Hexadecanoyl-γ-aminobutyricacid 2,5-dioxopyrrolidin-1-yl ester.

Ste-GABA-ONSu: N$^\gamma$-Octadecanoyl-γ-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester.

Purification and characterisation of acylated GLP-2 peptide analogs (GLP-2 derivatives):

The acylated analogs were purified using the following overall scheme:

	Step	Overall yield

1	GLP-2 peptide analog peptide	100%
	▼	
2	Acylation	77%
	▼	
3	RP-HPLC Column	63%
	▼	
4	Precipitation	58%
	▼	
5	Solubilization and freeze-drying	51%

The acylated analogs were characterised by mass spectrometry analysis as described.

Example 14.

Pharmaceutical formulations.

Buffer and optionally a preservative, optionally an isotonic agent, optionally further additive(s) selected from chelating agent, stabilizer (e.g. imidazole or certain amino acids (charged-basic) such as histidine or arginine) and surfactant are dissolved and pH is adjusted to the specified pH. Hereafter the GLP-2 compound is dissolved under slow stirring. The pH is adjusted to the specified using Sodium Hydroxide and/or Hydrochloric Acid. Finally, the formulation is sterilized by filtration through a 0.22 µm sterile filter.

Physical stability of the formulations is evaluated by means of visual inspection and turbidity after storage of the formulation in top filled glass cartridges for various time periods. The cartridges are stored at 5°C ± 3°C and/or at elevated temperatures (e.g. 25°C or 37°C).

Visual inspection of the formulations is performed in a sharp focused light with a dark background. The turbidity of the formulation is characterized by a visual score ranking the degree of turbidity from 0 to 3 (a formulation showing no turbidity corresponds to a visual score 0, and a formulation showing visual turbidity in daylight corresponds to visual score 3). A formulation is classified physical unstable with respect to protein aggregation, when it shows visual turbidity in daylight.

The turbidity is also measured in Nephelometric Turbidity Units (NTU) with a nephelometer, which has been calibrated with a Formazin standard. A formulation with a turbidity > 10 NTU is regarded as physical unstable.

GLP-2 compound concentrations are based on UV absorbance using $\varepsilon_{280} = 5700\ M^{-1}cm^{-1}$. Analytical HPLC. The contents of intact GLP-2 compound in samples is quantified by reverse phase HPLC using a C4 column and standard TFA/MeCN gradient elution.

The GLP-2 formulation may be evaluated by Equilibrium Solubility; a GLP-2 compound is dissolved at a concentration of 2 mg/mL in the appropriate buffer and the solution is filtered through a 0.45 µm filter. From the stock solution samples are withdrawn, the pH is adjusted to the desired value, and the samples are incubated at 23 °C for 24 hours. After centrifugation (20,000 g in 20 min at 23 °C) of each sample, pH is measured and the solubility estimated from measurement of the absorbance (or HPLC analysis) of the supernatant.

The GLP-2 formulation may also be evaluated by Accelerated stability testing; 2 mg/mL GLP-2 compound samples are prepared in buffers a-d and transferred to 0.2 mL HPLC vials which are sealed leaving "no" air-liquid interphase. Following incubation at defined temperatures in the 4-45 °C range, the content of intact GLP-2 compound as a function of time is determined by HPLC analysis.

The GLP-2 formulation may also be evaluated by Physical stability; The fluorescent dye thioflavine T (ThT) binds to the beta structure constituent of amyloid protein. The resulting increase in fluorescence quantum yield of the bound dye is used to predict the tendency of a GLP-2 compound to fibrillate under a variety of solvent conditions. Briefly, the GLP-2 compound is dissolved under the conditions of interest, a trace of ThT is added, the solutions are placed in 96-well microtiter plates where the fluorescence is read as a function of time using a predefined regimen of temperature and shaking conditions to effect accelerated amyloid formation. The resulting fluorescence vs time data then predicts the relative tendency of the GLP-2 compound to fibrillate under a set of conditions.

The GLP-2 formulation may also be evaluated by Analytical ultracentrifugation; Sedimentation velocity experiments are performed at 23 °C with a Beckman Optima XL-A ultracentrifuge equipped for simultaneous data capture using both absorbance and interference optics.

The GLP-2 formulation may also be evaluated by Circular Dichroism Spectroscopy. Far- and near-UV CD spectra are recorded at room temperature using a Jasco J-715 spectropolarimeter calibrated with (+)-10-camphorsulfonic acid.

Example 15.

Pharmaceutical formulations of GLP-2 derivatives.

Buffer and optionally a preservative, optionally an isotonic agent, optionally further additive(s) selected from chelating agent, stabilizer (e.g. imidazole or certain amino acids (charged-basic) such as histidine or arginine) and surfactant are dissolved and pH is adjusted to the specified pH. Hereafter the GLP-2 derivative is dissolved under slow stirring. The pH is adjusted to the specified using Sodium Hydroxide and/or Hydrochloric Acid. Finally, the formulation is sterilized by filtration through a 0.22 µm sterile filter.

Physical stability of the formulations is evaluated by means of visual inspection and turbidity after storage of the formulation in top filled glass cartridges for various time periods. The cartridges are stored at 5°C ± 3°C and/or at elevated temperatures (e.g. 25°C or 37°C).

Visual inspection of the formulations is performed in a sharp focused light with a dark background. The turbidity of the formulation is characterized by a visual score ranking the degree of turbidity from 0 to 3 (a formulation showing no turbidity corresponds to a visual score 0, and a formulation showing visual turbidity in daylight corresponds to visual score 3). A formulation is classified physical unstable with respect to protein aggregation, when it shows visual turbidity in daylight.

The turbidity is also measured in Nephelometric Turbidity Units (NTU) with a nephelometer, which has been calibrated with a Formazin standard. A formulation with a turbidity > 10 NTU is regarded as physical unstable.

GLP-2 derivative concentrations are based on UV absorbance using $\varepsilon_{280} = 5700\ M^{-1}cm^{-1}$. Analytical HPLC. The contents of intact GLP-2 derivative in samples is quantified by reverse phase HPLC using a C4 column and standard TFA/MeCN gradient elution.

The GLP-2 formulation may be evaluated by Equilibrium Solubility; a GLP-2 derivative is dissolved at a concentration of 2 mg/mL in the appropriate buffer and the solution is filtered through a 0.45 µm filter. From the stock solution samples are withdrawn, the pH is adjusted to the desired value, and the samples are incubated at 23 °C for 24 hours. After centrifugation (20,000 g in 20 min at 23 °C) of each sample, pH is measured and the solubility estimated from measurement of the absorbance (or HPLC analysis) of the supernatant.

The GLP-2 formulation may also be evaluated by Accelerated stability testing; 2 mg/mL GLP-2 derivative samples are prepared in buffers a-d and transferred to 0.2 mL HPLC vials which are sealed leaving "no" air-liquid interphase. Following incubation at defined temperatures in the 4-45 °C range, the content of intact GLP-2 derivative as a function of time is determined by HPLC analysis.

The GLP-2 formulation may also be evaluated by Physical stability; The fluorescent dye thioflavine T (ThT) binds to the beta structure constituent of amyloid protein. The resulting increase in fluorescence quantum yield of the bound dye is used to predict the tendency of a GLP-2 derivative to fibrillate under a variety of solvent conditions. Briefly, the GLP-2 derivative is dissolved under the conditions of interest, a trace of ThT is added, the solutions are placed in 96-well microtiter plates where the fluorescence is read as a function of time using a predefined regimen of temperature and shaking conditions to effect accelerated amyloid formation. The resulting fluorescence vs time data then predicts the relative tendency of the GLP-2 derivative to fibrillate under a set of conditions.

The GLP-2 formulation may also be evaluated by Analytical ultracentrifugation; Sedimentation velocity experiments are performed at 23 °C with a Beckman Optima XL-A ultracentrifuge equipped for simultaneous data capture using both absorbance and interference optics.

The GLP-2 formulation may also be evaluated by Circular Dichroism Spectroscopy. Far- and near-UV CD spectra are recorded at room temperature using a Jasco J-715 spectropolarimeter calibrated with (+)-10-camphorsulfonic acid.

Example 16.

Pharmaceutical lyophilized formulations.

When providing a lyophilized product, an essential feature relates to the properties of the lyophilized cake. It needs to have good properties as to its form and structure, i.e. it should not collapse in that such collapsed cakes can be hard or even impossible to dissolve (reconstitute) before use. Conversely, the physical structure of the lyophilized cake may not be too loosen and soft. Hence, pharmaceutical lyophilized formulations of GLP-2 and variants are produced using mannitol, sucrose (bulking agents), and glycylglycine (buffering agent) at the following final concentrations:

GLP-2 and variants:	0.001 - 0.1 mg/ml
Sucrose:	10 mg/ml
Mannitol:	37 mg/ml
Glycylglycine:	1.32 mg/ml

pH is adjusted to 8.00 ± 0.03 using 0.1N NaOH/HCl.

The solutions are filled in appropriate vials and lyophilized using standard lyophilisation methods as described by Wang et al, International Journal of Pharmaceutics 203 (2000): 1-60 (see section 4, page 16 ff.). Reconstitution of the lyophililised formulation is performed using an appropriate amount of water.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein (to the maximum extent permitted by law).

Any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context. For example, although many portions of the foregoing description focuses on methods for increasing the absorption of nutrients from the intestine in premature human infants having a condition associated with poor nutrient absorption from the intestine, it should be understood that these methods also can be used in other non-premature human infants and even adults (free from or suffering from similar conditions) as methods of increasing absorption of nutrients and/or inducing, promoting, and/or enhancing the treatment and/or prevention of gastrointestinal disorders. Additionally, several methods described herein are directed to compositions having specific advantageous features and several compositions are described herein that are advantageous for certain applications. It should be understood that such compositions described with reference to the methods of the invention and such applications of particular compositions of the invention are, in and of themselves, important features of the invention.

The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. Unless otherwise stated, all exact values provided herein are representative of corresponding approximate values.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should

be construed as indicating any non-claimed element as essential to the practice of the invention.

The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability, and/or enforceability of such patent documents.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law.

CLAIMS

1. A method for increasing the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine comprising administering to the infant a composition comprising a GLP-2 compound in a concentration of about 0.001-0.5 mg/ml in a volume sufficient to provide a detectable increase in absorption of nutrients from the intestine.

2. The method according to claim 1, wherein said concentration of the GLP-2 compound is from about 0.005 mg/ml to a concentration about 0.09 mg/ml, such as from about 0.01 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.02 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.03 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.04 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.05 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.06 mg/ml to a concentration about 0.08 mg/ml.

3. The method according to any of claims 1 or 2, wherein of the GLP-2 compound is present in the composition in an amount such that the infant will receive a dose of the GLP-2 compound of about 0.01 to about 8 mg/day.

4. The method according to any of claims 1-3, wherein said volume is from about 0.05 ml to about 5 ml, such as from about 0.1 ml to about 4 ml, such as from about 0.1 ml to about 3 ml, such as from about 0.1 ml to about 2 ml, such as from about 0.1 ml to about 1 ml, such as from about 0.1 ml to about 0.5 ml.

5. The method according to any of claims 1-4, wherein the body weight of said premature human infant is about 3 kg or less, such as below 2.5 kg, such as below 2.0 kg, such as below 1.5 kg, such as below 1 kg, such as below 0.8 kg, such as below 0.7 kg, such as below 0.6 kg.

6. The method according to any of claims 1-5, wherein said composition is administered by continuous injection.

7. The method according to any of claims 1-6, wherein said composition is administered by subcutaneous injection.

8. The method according to any of claims 1-6, wherein said composition is administered by intravenous injection.

9. The method according to any of claims 1-5, wherein said composition is administered by infusion.

10. The method according to any of claims 1-9, wherein said composition is a stable liquid formulation.

11. The method according to any of claims 1-9, wherein said composition is obtained by dissolving a predetermined amount of lyophilized composition comprising a GLP-2 compound in an aqueous or other pharmaceutically acceptable solution.

12. The method according to any of claims 1-9, wherein said composition is provided for by thawing a predetermined amount of frozen composition comprising a GLP-2 compound.

13. The method according to any of claims 1-12, wherein said GLP-2 compound is
S5K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)-GLP-2(1-33);

L17K(3-(tetradecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);

N24K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S5K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);

L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D3E/S5K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/S7K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D8K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/E9K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/M10K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N11K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/T12K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/I13K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L14K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D15K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N16K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(decanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K(3-(undecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(dodecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tridecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tetradecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(pentadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(heptadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(eicosanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K(4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/A18K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/D21K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/N24K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/Q28K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); GLP-2(1-33), 34R-GLP-2(1-34), A2G-GLP-2(1-33), A2G/34R-GLP-2(1-34), K30R-GLP-2(1-33); S5K-GLP-2(1-33); S7K-GLP-2(1-33); D8K-GLP-2(1-33); E9K-GLP-2(1-33); M10K-GLP-2(1-33); N11K-GLP-2(1-33); T12K-GLP-2(1-33); I13K-GLP-2(1-33); L14K-GLP-2(1-33); D15K-GLP-2(1-33); N16K-GLP-2(1-33); L17K-GLP-2(1-33); A18K-GLP-2(1-33); D21K-GLP-2(1-33); N24K-GLP-2(1-33); Q28K-GLP-2(1-33); S5K/K30R-GLP-2(1-33); S7K/K30R-GLP-2(1-33); D8K/K30R-GLP-2(1-33); E9K/K30R-GLP-2(1-33); M10K/K30R-GLP-2(1-33); N11K/K30R-GLP-2(1-33); T12K/K30R-GLP-2(1-33); I13K/K30R-GLP-2(1-33); L14K/K30R-GLP-2(1-33); D15K/K30R-GLP-2(1-33); N16K/K30R-GLP-2(1-33); L17K/K30R-GLP-2(1-33); A18K/K30R-GLP-2(1-33); D21K/K30R-GLP-2(1-33); N24K/K30R-GLP-2(1-33); Q28K/K30R-GLP-2(1-33); K30R/D33K-GLP-2(1-33); D3E/K30R/D33E-GLP-2(1-33); D3E/S5K/K30R/D33E-GLP-2(1-33); D3E/S7K/K30R/D33E-GLP-2(1-33); D3E/D8K/K30R/D33E-GLP-2(1-33); D3E/E9K/K30R/D33E-GLP-2(1-33); D3E/M10K/K30R/D33E-GLP-2(1-33); D3E/N11K/K30R/D33E-GLP-2(1-33); D3E/T12K/K30R/D33E-GLP-2(1-33); D3E/I13K/K30R/D33E-GLP-2(1-33); D3E/L14K/K30R/D33E-GLP-2(1-33); D3E/D15K/K30R/D33E-GLP-2(1-33); D3E/N16K/K30R/D33E-GLP-2(1-33); D3E/L17K/K30R/D33E-GLP-2(1-33); D3E/A18K/K30R/D33E-GLP-2(1-33); D3E/D21K/K30R/D33E-GLP-2(1-33); D3E/N24K/K30R/D33E-GLP-2(1-33); D3E/Q28K/K30R/D33E-GLP-2(1-33); or a combination of any thereof.

14. A composition comprising a GLP-2 compound in a concentration from about 0.001-0.1 mg/ml in a volume sufficient to detectably increase absorption of nutrients from the intestine of a premature human infant having an impaired ability to absorb nutrients from the intestine and a pharmaceutically acceptable carrier.

15. The composition according to claim 14, wherein the composition is a lyophilizable composition.

16. The composition according to claim 14 or claim 15, wherein said concentration is from about 0.005 mg/ml to a concentration about 0.09 mg/ml, such as from about 0.01 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.02 mg/ml to a concentration about

0.08 mg/ml, such as from about 0.03 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.04 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.05 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.06 mg/ml to a concentration about 0.08 mg/ml.

17. The composition according to any of claims 14-16, wherein said amount of a GLP-2 compound is sufficient to provide a dose of about 0.01 to 8 mg/day to at least a substantial proportion of a population of premature human infants.

18. The composition according to any of claims 14-17, wherein said volume is from about 0.05 ml to about 5 ml, such as from about 0.1 ml to about 4 ml, such as from about 0.1 ml to about 3 ml, such as from about 0.1 ml to about 2 ml, such as from about 0.1 ml to about 1 ml, such as from about 0.1 ml to about 0.5 ml.

19. The composition according to any of claims 17, wherein the body weight of the premature human infants in the population is about 3 kg or less, such as below 2.5 kg, such as below 2.0 kg, such as below 1.5 kg, such as below 1 kg, such as below 0.8 kg, such as below 0.7 kg, such as below 0.6 kg.

20. The composition according to any of claims 14-19, wherein said composition is formulated for administration by continuous injection.

21. The composition according to any of claims 14-19, wherein said composition is formulated for administration by subcutaneous injection.

22. The composition according to any of claims 14-19, wherein said composition is formulated for administration by intravenous injection.

23. The composition according to any of claims 14-19, wherein said composition is formulated for administration by infusion.

24. The composition according to any of claims 14-22, wherein said composition is a stable liquid formulation.

25. The composition according to any of claims 14-23, wherein said composition is a frozen composition comprising a GLP-2 compound.

26. The composition according to any of claims 14-26, wherein said GLP-2 compound is
S5K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);

L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S5K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)/K30R-GLP-2(1-33);

L17K(3-(nonanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);

L17K(4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D3E/S5K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/S7K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D8K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/E9K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/M10K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N11K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/T12K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/I13K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L14K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D15K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N16K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(decanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(undecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(dodecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tridecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tetradecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(pentadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(heptadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(eicosanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/L17K(4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33); D3E/A18K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/D21K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/N24K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); D3E/Q28K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); GLP-2(1-33), 34R-GLP-2(1-34), A2G-GLP-2(1-33), A2G/34R-GLP-2(1-34), K30R-GLP-2(1-33); S5K-GLP-2(1-33); S7K-GLP-2(1-33); D8K-GLP-2(1-33); E9K-GLP-2(1-33); M10K-GLP-2(1-33); N11K-GLP-2(1-33); T12K-GLP-2(1-33); I13K-GLP-2(1-33); L14K-GLP-2(1-33); D15K-GLP-2(1-33); N16K-GLP-2(1-33); L17K-GLP-2(1-33); A18K-GLP-2(1-33); D21K-GLP-2(1-33); N24K-GLP-2(1-33); Q28K-GLP-2(1-33); S5K/K30R-GLP-2(1-33); S7K/K30R-GLP-2(1-33); D8K/K30R-GLP-2(1-33); E9K/K30R-GLP-2(1-33); M10K/K30R-GLP-2(1-33); N11K/K30R-GLP-2(1-33); T12K/K30R-GLP-2(1-33); I13K/K30R-GLP-2(1-33); L14K/K30R-GLP-2(1-33); D15K/K30R-GLP-2(1-33); N16K/K30R-GLP-2(1-33); L17K/K30R-GLP-2(1-33); A18K/K30R-GLP-2(1-33); D21K/K30R-GLP-2(1-33); N24K/K30R-GLP-2(1-33); Q28K/K30R-GLP-2(1-33); K30R/D33K-

GLP-2(1-33); D3E/K30R/D33E-GLP-2(1-33); D3E/S5K/K30R/D33E-GLP-2(1-33); D3E/S7K/K30R/D33E-GLP-2(1-33); D3E/D8K/K30R/D33E-GLP-2(1-33); D3E/E9K/K30R/D33E-GLP-2(1-33); D3E/M10K/K30R/D33E-GLP-2(1-33); D3E/N11K/K30R/D33E-GLP-2(1-33); D3E/T12K/K30R/D33E-GLP-2(1-33); D3E/I13K/K30R/D33E-GLP-2(1-33); D3E/L14K/K30R/D33E-GLP-2(1-33); D3E/D15K/K30R/D33E-GLP-2(1-33); D3E/N16K/K30R/D33E-GLP-2(1-33); D3E/L17K/K30R/D33E-GLP-2(1-33); D3E/A18K/K30R/D33E-GLP-2(1-33); D3E/D21K/K30R/D33E-GLP-2(1-33); D3E/N24K/K30R/D33E-GLP-2(1-33); D3E/Q28K/K30R/D33E-GLP-2(1-33); or a combination of any thereof.

27. A kit for preparing a pharmaceutically acceptable composition for promoting the absorption of nutrients from the intestine comprising:

a first component comprising a predetermined lyophilized amount of a GLP-2 compound;

a second component different from the first component comprising a predetermined volume of a pharmaceutically acceptable aqueous solution;

whereby mixture of the first and second components results in a liquid pharmaceutically acceptable composition comprising a GLP-2 compound in a concentration from about 0.001 mg/ml to about 0.5 mg/ml and in a volume sufficient to increase the absorption of nutrients in a premature human infant having a condition associated with an impaired ability to absorb nutrients from the intestine.

28. The kit according to claim 27, wherein said second component contains a preservative consisting of chlorobutanol, benzyl alcohol, benzalkonium chloride, or a mixture of any thereof in an amount to sufficient provide a concentration of the preservative in the pharmaceutically acceptable composition of about 0.001 to about 2 w/v %.

29. The kit according to any of claims 27 or 28, wherein said concentration is from about 0.005 mg/ml to a concentration about 0.09 mg/ml, such as from about 0.01 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.02 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.03 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.04 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.05 mg/ml to a concentration about 0.08 mg/ml, such as from about 0.06 mg/ml to a concentration about 0.08 mg/ml.

30. The kit according to any of claims 27-29, wherein said volume is from about 0.05 ml to about 5 ml, such as from about 0.1 ml to about 4 ml, such as from about 0.1 ml to about 3 ml, such as from about 0.1 ml to about 2 ml, such as from about 0.1 ml to about 1 ml, such as from about 0.1 ml to about 0.5 ml.

31. The kit according to any of claims 27-30, wherein said GLP-2 compound is
S5K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N16K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)-GLP-2(1-33);

L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(hexadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)-GLP-2(1-33);
S5K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
S7K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D8K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
E9K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
M10K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N11K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
T12K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
I13K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L14K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D15K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);

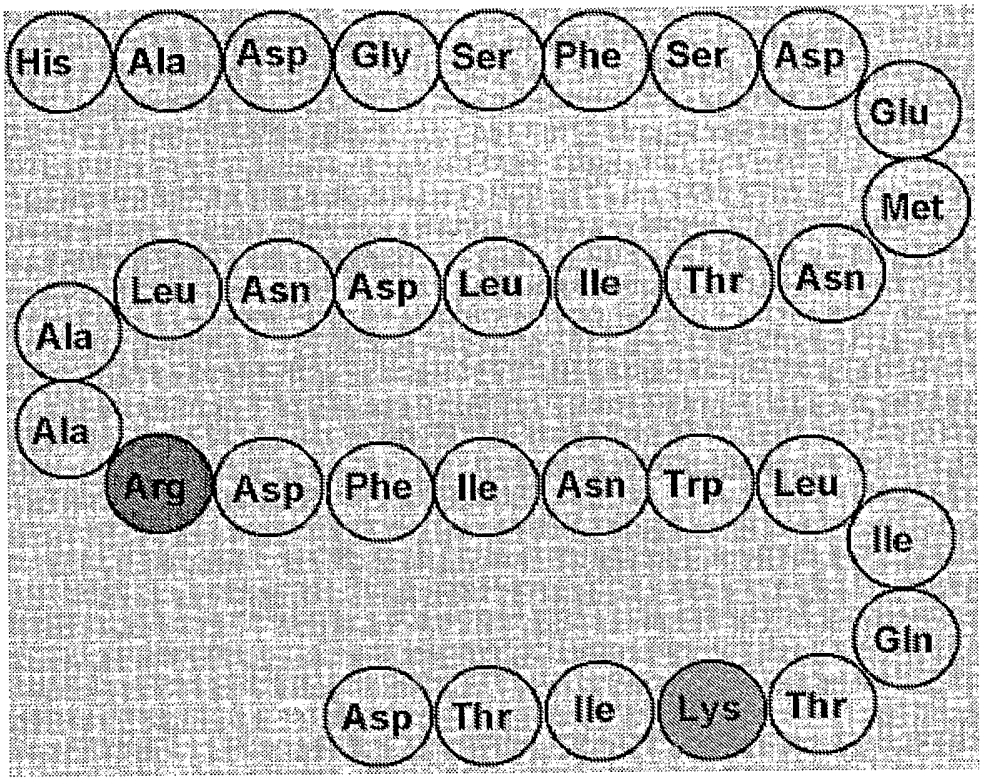
N16K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(decanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(undecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(dodecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tridecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(tetradecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(pentadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(heptadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(octadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(nonadecanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K(3-(eicosanoylamino)propionyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(decanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(undecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(dodecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tridecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(tetradecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(pentadecanoylamino)butanoyl)/K30R-GLP-2(1-33);

L17K(4-(hexadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(heptadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(octadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(nonadecanoylamino)butanoyl)/K30R-GLP-2(1-33);
L17K(4-(eicosanoylamino)butanoyl)/K30R-GLP-2(1-33);
A18K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D21K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
N24K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
Q28K(3-(hexadecanoylamino)propionyl)/K30R-GLP-2(1-33);
D3E/S5K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/S7K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D8K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/E9K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/M10K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N11K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/T12K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/I13K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L14K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D15K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N16K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(decanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(undecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(dodecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tridecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(tetradecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(pentadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(heptadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(octadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(nonadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(3-(eicosanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);

D3E/L17K((S)-4-carboxy-4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K((S)-4-carboxy-4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(decanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(undecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(dodecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tridecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(tetradecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(pentadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(hexadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(heptadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(octadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(nonadecanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/L17K(4-(eicosanoylamino)butanoyl)/K30R/D33E-GLP-2(1-33);
D3E/A18K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/D21K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/N24K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33);
D3E/Q28K(3-(hexadecanoylamino)propionyl)/K30R/D33E-GLP-2(1-33); GLP-2(1-33), 34R-GLP-2(1-34), A2G-GLP-2(1-33), A2G/34R-GLP-2(1-34), K30R-GLP-2(1-33); S5K-GLP-2(1-33); S7K-GLP-2(1-33); D8K-GLP-2(1-33); E9K-GLP-2(1-33); M10K-GLP-2(1-33); N11K-GLP-2(1-33); T12K-GLP-2(1-33); I13K-GLP-2(1-33); L14K-GLP-2(1-33); D15K-GLP-2(1-33); N16K-GLP-2(1-33); L17K-GLP-2(1-33); A18K-GLP-2(1-33); D21K-GLP-2(1-33); N24K-GLP-2(1-33); Q28K-GLP-2(1-33); S5K/K30R-GLP-2(1-33); S7K/K30R-GLP-2(1-33); D8K/K30R-GLP-2(1-33); E9K/K30R-GLP-2(1-33); M10K/K30R-GLP-2(1-33); N11K/K30R-GLP-2(1-33); T12K/K30R-GLP-2(1-33); I13K/K30R-GLP-2(1-33); L14K/K30R-GLP-2(1-33); D15K/K30R-

GLP-2(1-33); N16K/K30R-GLP-2(1-33); L17K/K30R-GLP-2(1-33); A18K/K30R-GLP-2(1-33); D21K/K30R-GLP-2(1-33); N24K/K30R-GLP-2(1-33); Q28K/K30R-GLP-2(1-33); K30R/D33K-GLP-2(1-33); D3E/K30R/D33E-GLP-2(1-33); D3E/S5K/K30R/D33E-GLP-2(1-33); D3E/S7K/K30R/D33E-GLP-2(1-33); D3E/D8K/K30R/D33E-GLP-2(1-33); D3E/E9K/K30R/D33E-GLP-2(1-33); D3E/M10K/K30R/D33E-GLP-2(1-33); D3E/N11K/K30R/D33E-GLP-2(1-33); D3E/T12K/K30R/D33E-GLP-2(1-33); D3E/I13K/K30R/D33E-GLP-2(1-33); D3E/L14K/K30R/D33E-GLP-2(1-33); D3E/D15K/K30R/D33E-GLP-2(1-33); D3E/N16K/K30R/D33E-GLP-2(1-33); D3E/L17K/K30R/D33E-GLP-2(1-33); D3E/A18K/K30R/D33E-GLP-2(1-33); D3E/D21K/K30R/D33E-GLP-2(1-33); D3E/N24K/K30R/D33E-GLP-2(1-33); D3E/Q28K/K30R/D33E-GLP-2(1-33); or a combination of any thereof.

Figure 1.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Gly
Ser
Phe
Ser
Asp
Glu
Met
Leu
Asn
Asp
Leu
Ile
Thr
Asn
Ala
Ala
Arg
Asp
Phe
Ile
Asn
Trp
Leu
Ile
Gln
Asp
Thr
Ile
Lys
Thr

Figure 2.

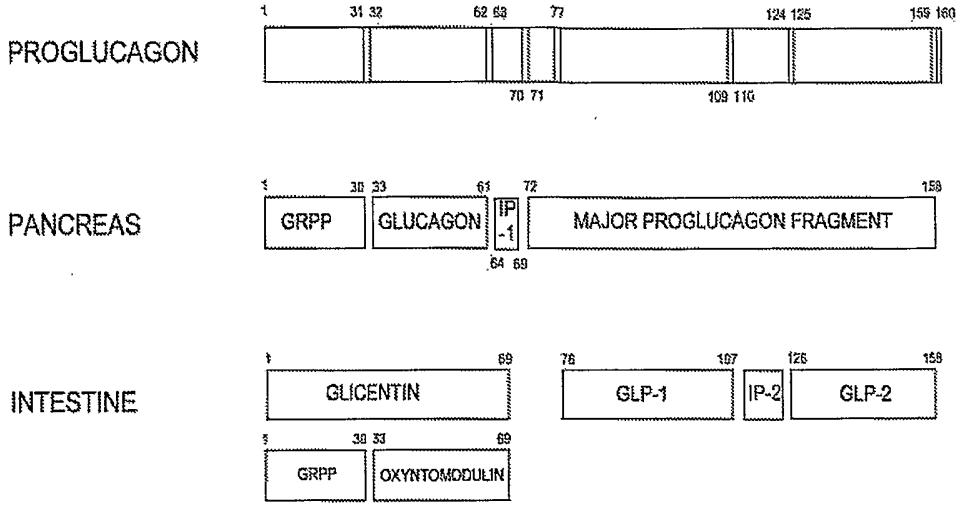

PROGLUCAGON
1
31 32
62 63
77
124 125
159 160
70 71
109 110
PANCREAS
1
30 33
61
72
158
GRPP
GLUCAGON
IP-1
MAJOR PROGLUCAGON FRAGMENT
64 69
INTESTINE
1
69
GLICENTIN
78
107
126
158
GLP-1
IP-2
GLP-2
1
30 33
69
GRPP
OXYNTOMODULIN

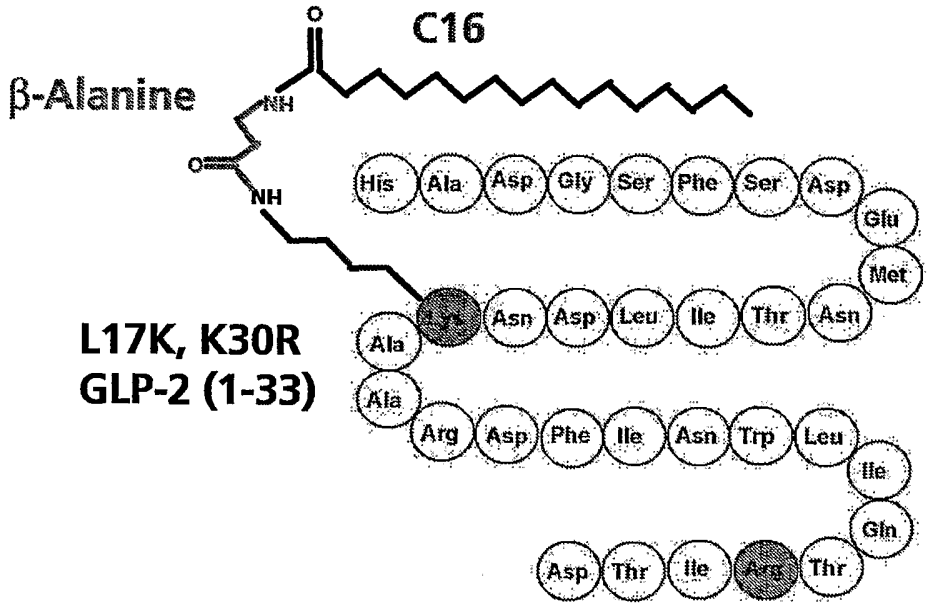
Figure 3.

Source	GLP-2 sequence	Accession no./ Ref. no.
Human	HADGSFSDEMNTILDNLAARDFINWLIQTKITD	P01275
Golden hamster	HADGSFSDEMNTILDSLATRDFINWLIQTKITD	P0127
Rat	HADGSFSDEMNTILDNLATRDFINWLIQTKITD	P06883
Guinea-pig	HADGSFSDEMNTILDNLATRDFINWLIQTKITD	P05110
Mouse	HADGSFSDEMSTILDNLATRDFINWLIQTKITD	P55095
Bovine	HADGSFSDEMNTVLDSLATRDFINWLLQTKITD	P01272
Pig	HADGSFSDEMNTVLDNLATRDFINWLLHTKITD	P01274
Degu (rodent)	HADGSFSDEMNTVLDHLATKDFINWLIQTKITD	P22890
Chicken	HADGTFTSDINKIIDDMAAKEFLKWLINTKVTQ	I51301
Frog	HADGSFTSDFNKALDIKAAQEFLDWIINTPVKE	Ref. 37
Salamander	HADGSFTSDINKVLDTIAAKEFLNWLISTKVTE	AAB37529
Trout	HVDGSFTSDVNKVLDSLAAKEYLLWVMTSKTSG	Ref. 37

Figure 4.

Tissue	F1 quantitation, copies per µg total RNA	β-Actin quantitation, copies per µg total RNA	GLP-2R/β-actin ratio
Jejunum	11,900	15,500,000	76.8×10^{-5}
Duodenum	9,150	85,700,000	10.7×10^{-5}
Ileum	7,490	51,400,000	14.6×10^{-5}
Colon	4,150	19,800,000	21.0×10^{-5}
Stomach	1,530	23,600,000	6.48×10^{-5}
Brain	<600	40,600,000	$<1.48 \times 10^{-5}$
Heart	<600	6,600,000	$<9.09 \times 10^{-5}$
Kidney	<600	14,900,000	$<4.03 \times 10^{-5}$
Liver	<600	16,700,000	$<3.59 \times 10^{-5}$
Lung	<600	38,500,000	$<1.56 \times 10^{-5}$
Muscle	<600	4,600,000	$<13.0 \times 10^{-5}$
Spleen	<600	44,800,000	$<1.34 \times 10^{-5}$

Figure 5.


C16
β-Alanine
NH
NH
L17K, K30R
GLP-2 (1-33)
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Ala
Asp
Gly
Ser
Phe
Ser
Asp
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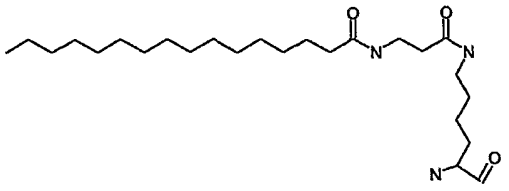
Met
Asn
Asp
Leu
Ile
Thr
Asn
Ala
Ala
Arg
Asp
Phe
Ile
Asn
Trp
Leu
Ile
Gln
Asp
Thr
Ile
Arg
Thr

Figure 6.

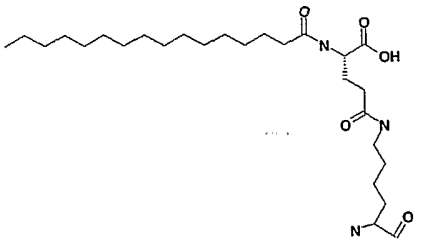
a) Example of the use of a β-alanine spacer on a lysine residue:

Lys(3-(hexadecanoylamino)propionyl):



b) Example of the use of a γ-glutamic acid spacer on a lysine residue:

Lys((S)-4-carboxy-4-(hexadecanoylamino)butanoyl):



c) Example of the use of a GABA spacer on a lysine residue:

Lys(4-(hexadecanoylamino)butanoyl):

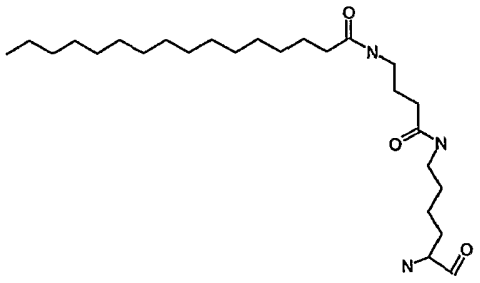
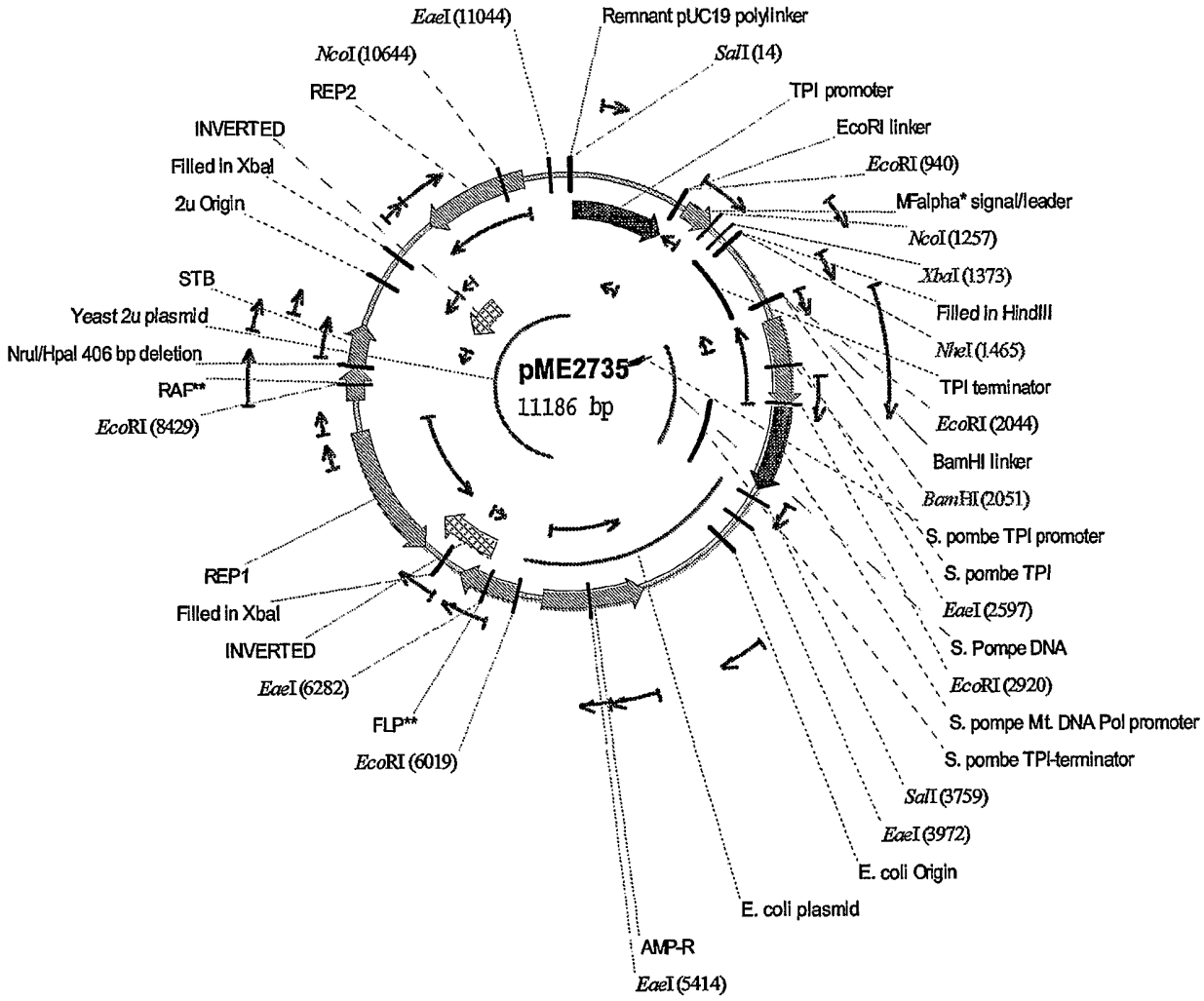


Figure 7.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11186 bp
EaeI (11044)
NcoI (10644)
REP2
INVERTED
Filled in XbaI
2u Origin
STB
Yeast 2u plasmid
NruI/HpaI 406 bp deletion
RAF**
EcoRI (8429)
REP1
Filled in XbaI
INVERTED
EaeI (6282)
FLP**
EcoRI (6019)
AMP-R
EaeI (5414)
E. coli plasmid
E. coli Origin
EaeI (3972)
SalI (3759)
S. pombe TPI-terminator
S. pombe Mt. DNA Pol promoter
EcoRI (2920)
S. Pompe DNA
EaeI (2597)
S. pombe TPI
S. pombe TPI promoter
BamHI (2051)
BamHI linker
EcoRI (2044)
TPI terminator
NheI (1465)
Filled in HindIII
XbaI (1373)
NcoI (1257)
MFalpha* signal/leader
EcoRI (940)
EcoRI linker
TPI promoter
SalI (14)
Remnant pUC19 polylinker

Figure 8.

SEQ ID NO. 1 (The amino acid sequence of native human GLP-2(1-33)):

H A D G S F S D E M N T I L D N L A A R D F I N W L I Q T K I T D

SEQ ID NO. 2 (GLP-2 peptides according to formula I):

His-X^2-X^3-Gly-X^5-Phe-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-X^{18}-Ala-Arg-X^{21}-Phe-Ile-X^{24}-Trp-Leu-Ile-X^{28}-Thr-Arg-Ile-Thr-X^{33}-X^{34}

wherein X^2 is Ala, Val or Gly; X^3 is Asp, or Glu; X^5 is Ser, or Lys; X^7 is Ser, or Lys; X^8 is Asp, Glu, or Lys; X^9 is Asp, Glu, or Lys; X^{10} is Met, Lys, Leu, Ile, or Nor-Leucine; X^{11} is Asn, or Lys; X^{12} is Thr, or Lys; X^{13} is Ile, or Lys; X^{14} is Leu, or Lys; X^{15} is Asp, or Lys; X^{16} is Asn, or Lys; X^{17} is Leu, or Lys; X^{18} is Ala, or Lys; X^{21} is Asp, or Lys; X^{24} is Asn, or Lys; X^{28} is Gln, or Lys; X^{33} is Asp, Glu, or Lys; X^{34} is OH, Lys, Arg, Arg-Lys, Lys-Arg, Arg-Arg, or Lys-Lys.

.

SEQ ID NO. 3 (GLP-2 peptides according to formula II):

His-X^2-X^3-Gly-X^5-Phe-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-X^{18}-Ala-X^{20}-X^{21}-Phe-Ile-X^{24}-Trp-Leu-Ile-X^{28}-Thr-X^{30}-Ile-Thr-X^{33}-X^{34}

wherein X^2 is Ala, Val or Gly; X^3 is Asp, or Glu; X^5 is Ser, or Lys; X^7 is Ser, or Lys; X^8 is Asp, Glu, or Lys; X^9 is Asp, Glu, or Lys; X^{10} is Met, Lys, Leu, Ile, or Nor-Leucine; X^{11} is Asn, or Lys; X^{12} is Thr, or Lys; X^{13} is Ile, or Lys; X^{14} is Leu, or Lys; X^{15} is Asp, or Lys; X^{16} is Asn, or Lys; X^{17} is Leu, or Lys; X^{18} is Ala, or Lys; X^{20} is Arg, or Lys; X^{21} is Asp, or Lys; X^{24} is Asn, or Lys; X^{28} is Gln, or Lys; X^{30} is Arg, or Lys; X^{33} is Asp, Glu, or Lys; X^{34} is OH, Lys, Arg, Arg-Lys, Lys-Arg, Arg-Arg, or Lys-Lys.