Filed on behalf of Petitioner COALITION FOR AFFORDABLE DRUGS II LLC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS II LLC
Petitioner

v.

NPS PHARMACEUTICALS, INC.
Patent Owner

Case No. To Be Assigned
Patent No. 7,056,886

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,056,886 (CLAIMS 46-52 and 61-75) UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.*

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I. INTRODUCTION

Coalition for Affordable Drugs II LLC ("Petitioner" or "CFAD") respectfully requests an *Inter Partes* ("IPR") review for Claims 46-52 and 61-75 of U.S. Patent No. 7,056,886, issued on June 6, 2006, to Isaacs ("the '886 patent") (Ex. 1003) in accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.*

Independent claims 46 and 52 are directed to a formulation containing a peptide known as "glucagon-like peptide-2" ("GLP-2") or an analog thereof. Independent claim 61 is directed to a kit containing the same GLP-2 formulation along with a vial of sterile water and instructions. Independent claim 69 is directed to a method of treatment comprising administering a GLP-2 formulation to effect the growth or functioning of the gastrointestinal tract. There is a reasonable likelihood that at least one of these independent claims and those claims depending therefrom are unpatentable because they would have been obvious to a person of ordinary skill in the art.

Formulations of GLP-2 and therapeutic use of such formulations for treatment of gastrointestinal disorders were well known before the earliest effective filing date of the '886 patent. Storage stable formulations of a related peptide, glucagon, were also disclosed in the prior art. As shown herein, the

combination of the cited prior art references discloses all of the limitations of the claimed GLP-2 formulation, methods, and kits.

A person of ordinary skill in the art would have been motivated to combine these prior art references in order to form a stable GLP-2 formulation for therapeutic use because there was a known design need for storage stable formulations. It was known that formulations of peptides, including peptides such as glucagon, lack storage stability. A solution to this problem, provided by the prior art, was to add L-histidine and sucrose or mannitol to the formulation to increase storage stability. Furthermore, GLP-2 and glucagon disclosed in the prior art are structurally similar leading one of ordinary skill in the art to combine disclosures in the prior art references with a view to forming a stable GLP-2 formulation.

The combination of the prior art also provides a reasonable expectation of success in formulating GLP-2 in combination with L-histidine and sucrose or mannitol to create a storage stable formulation. Through routine experimentation, a person of ordinary skill in the art would easily substitute active ingredients having a similar physical and chemical profile to glucagon into stable formulations disclosed in the cited art. At the very least, storage stable formulations taught in the prior art for glucagon would be obvious to try with GLP-2.

The claimed subject matter represents nothing more than the predictable use of known components having known functions, and represents a strong case for obviousness that overcomes any evidence of secondary considerations. The Patentee has not argued and cannot argue that the claimed subject matter provides unexpected results because similar results are shown for storage stable formulations of glucagon in the cited prior art. To the extent Patentee alleges commercial success to rebut the obviousness of claims 46- 52 and 69-75, no nexus between these claims and any alleged commercial success exists.

Thus, the formulations of GLP-2, the claimed kit to deliver the GLP-2 formulation as well as the claimed method of administering the GLP-2 formulation are obvious given the state of the art before the filing date of the '886 patent. It is on this basis that claims 46-52 and 61-75 of the '886 patent are not directed to anything inventive and merely demonstrate an attempt to capture that which was already in the prior art. As a result, claims 46-52 and 61-75 are unpatentable and an IPR should be instituted on this basis.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8

A. Real Party-In-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Coalition For Affordable Drugs II LLC ("CFAD"), Hayman Credes Master Fund, L.P. ("Credes"), Hayman Orange Fund SPC – Portfolio A ("HOF"), Hayman Capital

Master Fund, L.P. (“HCMF”), Hayman Capital Management, L.P. (“HCM”), Hayman Offshore Management, Inc. (“HOM”), Hayman Investments, L.L.C. (“HI”), nXn Partners, LLC (“nXnP”), IP Navigation Group, LLC (“IPNav”), J Kyle Bass, and Erich Spangenberg are the real parties in interest (collectively, “RPI”). The RPI hereby certify the following information: CFAD is a wholly owned subsidiary of Credes. Credes is a limited partnership. HOF is a segregated portfolio company. HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HCM is the investment manager of HOF. HOM is the administrative general partner of Credes and HCMF. HI is the general partner of HCM. J Kyle Bass is the sole member of HI and sole shareholder of HOM. CFAD, Credes, HOF and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes, HOF and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is 98.5% member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the 98.5% member of IPNav. Other than HCM and J Kyle Bass in his capacity as the Chief Investment Officer of HCM and nXnP and Erich Spangenberg in his capacity as the Manager/CEO of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD, Credes, HOF, HCMF, HCM, HOM, HI, nXnP or IPNav) has authority to direct or control (i) the timing of, filing of,

content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition will be borne by HCM, CFAD, Credes, HOF and/or HCMF.

B. Related Matters

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner is not aware of any judicial or administrative matters that could affect, or be affected by, a decision in this proceeding.

C. Lead and Backup Counsel

Lead Counsel:	**Backup Counsel:**
Jeffrey D. Blake, Esq. Registration No. 58,884 MERCHANT & GOULD P.C. 191 Peachtree Street N.E. Suite 4300 Atlanta, GA 30303 Main Telephone: (404) 954-5100 Main Facsimile: (404) 954-5099 jblake@merchantgould.com	Matthew L. Fedowitz, Esq. Registration No. 61,386 MERCHANT & GOULD P.C. 1701 Duke Street, Suite 310 Alexandria, VA 22314 Main Telephone: (703) 684-2500 Main Facsimile: (703) 684-2501 mfedowitz@merchantgould.com Katherine M. Kowalchyk, Esq. Registration No. 36,848 Brent E. Routman (*Pro Hac Vice*) MERCHANT & GOULD P.C. 3200 IDS Center 80 South Eighth Street Minneapolis, MN 55402 Main Telephone: (612) 332-5300 Main Facsimile: (612) 322-9081 kkowalchyk@merchantgould.com broutman@merchantgould.com

A Power of Attorney is being filed concurrently herewith in accordance with 37 C.F.R. § 42.10(b).

D. Service Information

Papers concerning this matter should be served by EXPRESS MAIL, hand-delivery, or electronic mail at the following addresses:

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III. PAYMENT OF FEES

Payment of $26,200.00 for the fees set forth in 37 C.V.R. § 42.15(a)(1-4) for this Petition for *Inter Partes* Review accompanies this request by way of credit card payment. Twenty-two claims are challenged and excess claim fees in the amount of $400.00 (under 37 C.F.R. § 42.15(a)(3)) and $2,800 (under 37 C.F.R. § 42.15(a)(4)) are included. The undersigned further authorizes payment for any additional fees that might be due in connection with this Petition to be charged to Deposit Account No. 13-2725.

IV. REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing

Pursuant to 37 C.F.R. § 42.104(a), Petitioner hereby certifies that the '886 patent is available for *Inter Partes* review in accordance with 37 C.F.R. § 42.102(a)(2), and that the Petitioner is not barred or estopped from requesting *Inter Partes* review challenging the claims of the '886 patent on the grounds identified in this Petition. Neither Petitioner nor any privy of Petitioner has received a final written decision under 35 U.S.C. § 318(a) with respect to any claim of the '886 patent on any ground that was raised or could have been raised by Petitioner or its privies in any *Inter Partes* review, post grant review, or covered business method patent review.

B. Identification of Challenge and Precise Relief Requested

Pursuant to 37 C.F.R. § 42.104(b), Petitioner challenges Claims 46-52 and 61-75 of the '886 patent and requests that these claims be found unpatentable over the prior art for the reasons given herein.

1. Claims for Which *Inter Partes* Review is Requested

Petitioner requests *Inter Partes* review of Claims 46-52 and 61-75 of the '886 patent. The claims of the '886 patent at issue are directed to GLP-2 peptide formulations (claims 46-52), a kit containing a GLP-2 formulation (claims 61-68) ,

and a method of treatment using GLP-2 compositions (claims 69-75). Claims 46, 52, 61, and 69 are independent claims. Claims 47-51 all depend directly or indirectly from Claim 46. Dependent Claims 62-68 all depend either directly or indirectly from claim 61. Dependent Claims 70-75 all depend either directly or indirectly from Claim 69.

2. Statutory Ground on Which the Challenge is Based

Claims 46-52 and 69-75 are unpatentable because they are obvious under 35 U.S.C. § 103(a) in view of the combined teachings of U.S. Patent No. 5,789,379 to Drucker et al. ("Drucker '379") (Ex. 1029), U.S. Patent No. 5,652,216 to Kornfelt *et al.* ("Kornfelt") (Ex. 1027), Osterberg et al., "Physical State of L-histidine after Freeze Drying and Long Term Storage," European Journal of Pharmaceutical Sciences 8(1999)301-308 ("Osterberg") (Ex.1030), and Munroe *et al.*, Prototypic G-protein coupled receptor for the intestinotrophic factor glucagon –like peptide 2, Proc. Nat'l Acad. Sci. 96:1569 (1999)("Munroe")(Ex. 1022). Claims 61-68 are unpatentable because they would have been obvious under 35 U.S.C. § 103(a) in view of the combined teachings of PCT Publication W098/52600 to Drucker ("Drucker '600") (Ex. 1028), U. S. Patent No. 5,496,801 to Holthuis et al, ("Holthuis")(Ex. 1005), Kornfelt, Osterberg, and Munroe.

3. Evidence Relied Upon to Support the Challenge

Petitioner relies upon each of the publications cited herein. Each of these publications has a publication date more than one year prior to the '886 patent's effective filing date of December 30, 2000. On this basis, they are available as prior art under 35 U.S.C. § 102 (b). Petitioner also relies upon the Declaration of Dr. Anthony Palmieri III, Ph.D., R.Ph., an Associate Scholar of Pharmaceutics at the University of Florida College of Pharmacy (Ex. 1001), and the documents cited therein (Exs. 1002-1030), including Dr. Palmieri's *curriculum vitae* (Ex. 1002).

4. How the Challenged Claims Are to be Construed

The terms of the claims of the '886 patent are to be given their broadest reasonable interpretation in light of the specification, as understood by a person of ordinary skill in the art. *See* 37 C.F.R. § 42.100(b).

An "analog" of GLP-2 is construed to mean a peptide that incorporates one or more amino acid substitutions, deletions, additions, or modifications into a natural GLP-2 peptide and retains biological activity (Ex. 1003 at 4:33-36, 1:30-37; Ex. 1001 at ¶ 26). During prosecution, the Applicant overcame an indefiniteness rejection by confirming that term "analog" conformed to this definition (Ex. 1008 at 3; Ex. 1001 at ¶ 26). Similarly, Applicant stated that "biological activity" means that "GLP-2 and analogs thereof act as trophic agents to enhance and maintain the functioning of the gastrointestinal tract and to promote

the growth of intestinal tissue" to overcome a similar indefiniteness rejection (Ex. 1008 at 4; Ex. 1001 at ¶ 26).

"Medically useful amount" is defined in the specification to mean an amount of GLP-2 or analog thereof that ranges from a few micrograms to milligrams. This amount includes the ranges specified in the specification of about 0.1 to about 50 mg/ml of GLP-2, preferably about 5 to about 40 mg/ml, more preferably about 7 to about 30 mg/ml, even more preferably about 10 to about 20 mg/ml, and most preferably about 20 mg/ml (Ex. 1003 at 2:14-19,5:59-61, 6:12-19; Ex. 1001 at ¶ 27).

"Medically useful amount" or "medically effective amount is construed to mean an amount which is useful either therapeutically or diagnostically (Ex. 1003 at 5:59-61; Ex. 1001 at ¶ 27).

"Therapeutically effective amount" is defined in the specification to mean an amount of GLP-2 or analog thereof including unit dosage amounts useful to treat a subject including multidose amounts (Ex. 1003 at 5:64-67, 6:5-7; Ex. 1001 at ¶ 28).

"An amount sufficient to adjust the pH of the formulation to a physiological tolerable level" is defined in the '886 specification, to mean an amount that buffers the formulation to a pH that elicits reactions, in a recipient, that are not so extreme to preclude further administration of the formulation (Ex. 1003 at 5:45-51;

Ex. 1001 at ¶ 29). The specification states that this includes a pH of greater than about 5.5, more preferably greater than about 6, even more preferably of about 6.9 to about 7.9, and most preferably about 7.3 to about 7.4 (Ex. 1003 at 5:52-56; Ex. 1001 at ¶ 29).

"An amount sufficient to adjust the pH of the formulation to a pharmaceutically tolerable level" refers to an exemplary pH of "above about 6.0" as set forth in the specification (Ex. 1003 at 2:9-11; Ex. 1001 at ¶ 30).

"An amount sufficient to stabilize the formulation" is defined in the specification, as an amount of histidine that increases "the length of time that the GLP-2 peptide remains intact prior to degradation" (Ex. 1003 at 5:30-32; Ex. 1001 at ¶ 31). This amount includes 0.5 to 1% histidine (Ex. 1003 at 6:25-26; Ex. 1001 at ¶ 31). The specification specifies that the formulation when reconstituted from a lyophilized form is stable at least about 12 hours and preferably up to 24 hours at 4°C (Ex. 1003 at 7:1-3; Ex. 1001 at ¶ 31). Stability of GLP-2 or analogs thereof is measured by determining the purity and quantity of the peak of GLP-2 using reverse phase high pressure liquid chromatography. (Ex. 1003 at 9:65 to10:8; Ex. 1001 at ¶ 31).

V. SUMMARY OF THE '886 PATENT

A. Lineage of the '886 patent

The '886 patent is entitled "GLP-2 Formulations." (Ex. 1003, Cover page.)

The ’886 patent issued on June 6, 2006, from U.S. Patent Application Serial No. 09/750,022, filed on December 29, 2000 (“the ’022 application”) (Ex. 1003. Cover page). The ’022 application claims priority to Great Britain Patent Application No. 9930882 (Ex. 1003, Cover Page), filed on December 30, 1999.

B. Litigation Relating to the ’886 patent

The ’886 patent is not subject to any pending litigation of which Petitioner is aware.

C. Examination of the ’886 patent

Relevant portions of the file history of ’886 patent are presented herein. The ’886 patent issued from the ’022 application, filed on December 29, 2000. Before allowance, the Examiner issued three Non Final Actions, a Final Action that was withdrawn, followed by another Non Final Action. The claim rejections asserted by the Examiner were based on indefiniteness and obviousness. The obviousness rejections were overcome by the Applicant arguing that there was no motivation to combine the uncontested prior art cited.

A first Non-Final Office Action issued on March 8, 2002 (Ex. 1007). The Examiner rejected claims 1-54 under 35 U.S.C. § 112, second paragraph finding many claim terms indefinite (Ex. 1007 at 3-4). The indefinite terms included: “GLP-2;” “an analog;” “one or more amino acid substitutions, addition, deletions or modifications;” “biological activity;” claiming pH ranges with the term “about;”

"less than about;" "for up to at least;" "up to about 24 hours;" and "a disorder, disease or condition" (*Id*.). The Office Action *did not* include any rejections based on prior art. Applicant filed an Amendment and Reply on June 10, 2002, addressing the indefiniteness rejections (Ex. 1008).

A second Non-Final Office Action issued on February 5, 2003 (Ex. 1009). There, the Examiner rejected the claims as being obvious over a combination of Knudsen (WO 99/043361) (Ex. 1025) and Makino (U.S. Patent No. 4,985,244) (Ex.1026) (Ex. 1009 at 3). The Examiner supplemented the obviousness rejection by citing to Hora *et al.*, (US Patent No.5,997,856) Drucker *et al*. (WO 97/39031) Thim *et al*. (U.S. Patent No. 5,912,229) and Drucker (U.S. Patent No. 5,952,301) to reject claims 1-22, 31, 43-46, and 49-54 (*Id*. at 4-7).

Applicant filed an Amendment and Reply on July 9, 2003, where it was argued that the Examiner had not demonstrated a motivation to combine or a reasonable expectation of success in view of the combination of Knudsen and Makino (Ex. 1010 at 4-5). Notably, Applicant did not challenge the contention that the combination of the references disclosed all of the limitations of the claims (*Id.* at 4-5.).

A third Non-Final Office Action issued on September 16, 2003 (Ex. 1011). The Examiner once again rejected numerous claims as indefinite (Ex. 1011 at 3-5.). The Examiner rejected claims 1-22, 31-33,43-46, and 49-55 as obvious in view

of Knudsen (Ex. 1025) in combination with Yamazaki *et al.* (U.S. Patent No. 6,120,761) (Ex. 1006) (Ex. 1011 at 5-6) and the same supplementary references as the previous obviousness rejection.

In response, Applicant filed an Amendment and Reply on March 16, 2004 (Ex. 1012). Applicant once again argued that the Examiner had not demonstrated a motivation to combine the prior art references and was using an improper "obvious to try" standard (*Id.* at 15-1.). Applicant argued that one of skill in the art would not have been motivated to design a formulation for GLP-2 peptides because of differences between the erythropoietin protein of Yamazaki and GLP-2 (*Id.*).

A Final Office Action issued on June 8, 2004 with the Examiner allowing numerous claims and rejecting a number of others as indefinite under 35 U.S.C. §112, second paragraph (Ex. 1013). Applicant filed an Amendment and Reply on September 7, 2004 arguing the claims were not indefinite (Ex. 1014).

The Final Office Action was surprisingly withdrawn, and a fourth Non-Final Office Action issued on October 4, 2004, with the Examiner rejecting a number of claims as indefinite and as being obvious (Ex. 1015). The Examiner rejected claims 1-22, 43-46, and 73-78 using Knudsen (Ex. 1025) in combination with Kornfelt (U.S. Patent No. 5,652,216) (Ex. 1027) and the same supplementary references as previously discussed (*Id*. at 4-5).

Applicant filed an Amendment and Reply on January 4, 2005, arguing that

the Examiner had failed to demonstrate a motivation to combine the prior art cited and that the claims would not be indefinite to one of skill in the art (Ex. 1016). Applicant argued that there would be no reason to combine Knudsen and Kornfelt, despite the fact that Kornfelt expressly disclosed histidine stabilized glucagon formulations, and that glucagon and GLP-2 were known to be related peptides (*Id*. at 15-16). Applicant argued that GLP-2 differs from glucagon in sequence and in solubility in water at a pH of 2-4(*Id*. at 16). Applicant further argued that one of ordinary skill in the art would not attempt to design a formulation for GLP-2 based on Kornfelt without providing any evidence or expert declaration that the differences in amino acid sequence or solubility would affect the structure or stability of GLP-2 in a formulation as taught by Kornfeld (*Id.* at 17).

On April 4, 2005, a Notice of Allowance issued for claims 1-51, 53-55, and 58-78 of the ’022 application (Ex. 1017). The alleged reasons for allowance were:

> Knudsen *et al.* (WO 99/43361) teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of histidine or sodium phosphate, a pharmaceutical acceptable carrier, a preservative and a surfactant; Kornfelt *et al.* (U.S. Patent 5,652,216) disclose using stabilizing amount of a pharmaceutically acceptable ampholyte such as glycine, histidine or GlyGly in a pharmaceutical preparation comprising glucagons. However, Knudsen *et al.* either alone or in combination with Kornfelt *et al.* do not teach or suggest a GLP-2 formulation comprising a medically useful amount of GLP2 or an analog thereof, a phosphate buffer, L-histidine for stabilizing the formulation and a bulking agent of mannitol and sucrose.

(*Id.*at 2).

The ’022 application issued as the ’886 patent on June 6, 2006 (Ex. 1003).

D. Overview of the Cited Prior Art and the State of the Art

Formulations of GLP-2, methods of using formulations of GLP-2, and kits containing GLP-2 formulations were known prior to the effective filing date of the’886 patent (Ex. 1028 at p. 19:15-36; Ex. 1001 at ¶ 35). Drucker ’600 describes formulations of GLP-2 and analogs for use in promoting the proliferation of intestinal tissue (Ex. 1028 at p. 2:25-32; Ex. 1001 at ¶ 35). Biologically active analogs of GLP-2 with amino acid substitutions were also known as described extensively in Drucker ’379 (Ex.1029 at p. 4:6-7:20, p. 15:1-35; Ex. 1001 at ¶ 35). Drucker ’379 teaches that GLP-2 was known to be susceptible to DPP-IV cleavage (Ex.1029 at p. 6:36-45; Ex. 1021 at 675; Ex. 1001 at ¶ 35). This led to the development of analogs with replacement of an amino acid at position 2; the DPP-IV cleavage site (Ex.1029 at p. 6:36-45; Ex. 1001 at ¶ 35). One such analog of human GLP-2, h[Gly^2]GLP-2, was shown to be effective in an animal model of colitis (Ex. 1023 at G79; Ex. 1001 at ¶ 35). Munroe shows that GLP-2 analogs that stimulate intestinal cell proliferation were also known to bind to the GLP-2 receptor (Ex.1022 at 1573, Table 2; Ex. 1001 at ¶ 35).

It was known that GLP-2 was structurally related to glucagon. GLP-2 is a peptide hormone member of the glucagon superfamily of peptide hormones and has been described in the prior art since the 1980s (Ex. 1018 at 879; Ex. 1001 at ¶

36). GLP-2 and glucagon are generated from a single precursor, proglucagon, produced in intestinal enteroendocrine cells (Ex. 1018 at 885, Figure 8b; Ex. 1001 at ¶ 36). GLP-2 exhibits 50% amino acid sequence similarity to glucagon and has a similar molecular weight (Ex. 1018 at 879, Fig.3; Ex. 1001 at ¶ 36). Despite some differences in amino acid sequence, glucagon (Ex.1019 at 254, Table V) and GLP-2 (Ex. 1025 at p. 3:1-10; Ex. 1001 at ¶ 36) share a secondary structural feature of an alpha helix region. Analogs of GLP-2 retain the alpha helix motif and as well as binding capacity to the GLP-2 receptor (Ex.1022 at 1573, Table 2; Ex. 1020 at 8888, Abstract; Ex. 1001 ¶ 36).

It was known that pharmaceutical formulations of peptides for therapeutic use need to be storage stable (Ex.1024 at 8; Ex. 1001 at ¶ 37). At the time of filing of the ’886 patent, as taught by Osterberg, it was standard in the art to prepare a lyophilized formulation to improve storage stability of pharmaceutical compositions containing a peptide (Ex.1030 at 301; Ex. 1001 at ¶ 37). L-Histidine was well known as a buffer and a stabilizing agent useful in lyophilized pharmaceutical formulations of peptides such as glucagon as shown by Kornfelt (Ex.1027 at 2:28-38; Ex. 1001 at ¶ 37). Likewise, sucrose and mannitol were both well known as conventional bulking agents or excipients in the art of pharmaceutical formulations prior to the effective filing date of the ‘886 patent as described in Osterberg and Kornfelt (Ex. 1027 at 2:43-57; Ex.

1030 at 301; Ex. 1001 at ¶ 38). As demonstrated by Holthuis, kits including formulations of peptides prepared for injection would include a vial of water and an injection device (Ex. 1005 at 5:28-36; Ex. 1001 at ¶ 185).

VI. PETITIONER HAS A REASONABLE LIKELIHOOD OF PREVAILING

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Underlying factual determinations in an obviousness analysis include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of nonobviousness. *See Merck & Co. v. Teva Pharms. USA, Inc*., 395 F.3d 1364, 1369 (Fed. Cir. 2005) (citing *Graham v. John Deere Co*., 383 U.S. 1, 17-18 (1966)). The scope and content of the prior art, the level of ordinary skill in the art, and the differences between the claimed invention and the art relevant to this Petition are addressed for each statutory ground of rejection upon which this Petition is based.

In this regard, *Inter Partes* Review of the claims identified below is requested on the grounds that these claims are unpatentable for failing to meet the

requirements of 35 U.S.C. § 103(a). Copies of the references rendering these claims unpatentable are filed herewith. 37 C.F.R. § 42.6(c). These grounds for unpatentability are supported by the Declaration of Dr. Palmieri (Ex. 1001).

Ground	35 U.S.C.	Claims	Index of References
1	103(a)	46-50, 52 and 69-74	Drucker '379 (Ex. 1029) in view of Kornfelt (Ex. 1027) , and Osterberg (Ex. 1030).
2	103(a)	61-67	Drucker '600 (Ex. 1028) in view of Kornfelt (Ex. 1027), Osterberg (Ex. 1030), and Holthuis (Ex.1005).
3	103(a)	51 and 75	Drucker '379 (Ex. 1029) in view of Kornfelt (Ex. 1027), Osterberg (Ex. 1030), and Munroe (Ex. 1022).
4	103(a)	68	Drucker '600 (Ex. 1028) in view of Kornfelt (Ex. 1027), Osterberg (Ex. 1030), Munroe (Ex.1022) and Holthuis (Ex. 1005).

For each asserted ground, Petitioner can demonstrate where each limitation either exists in the prior art and/or is rendered obvious, by evaluating the scope and content of the prior art, any differences between the art and the challenged claims, the knowledge of a person of ordinary skill in the art and, and any available objective indicia of nonobviousness in accordance with *Graham v. John Deere Co.*, 383 U.S. 1 (1966) and *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007).

A. Each Reference Relied on for Grounds 1-4 Is Prior Art.

1. Ground 1: Claims 46-50, 52, and 69-75 are obvious in view of Drucker ’379 (Ex. 1029) and further in view of Kornfelt (Ex. 1027), and Osterberg (Ex. 1030).

Each reference applied in Ground 1 is prior art under 35 U.S.C. § 102(b) because each was published more than one year prior to the earliest effective filing date of the ’886 patent, which is December 29, 2000. Drucker ’379 (Ex. 1029) qualifies as a 102(b) reference because it is a U.S. Patent that published and issued on August 4, 1998. Kornfelt (Ex. 1027) qualifies as a 102(b) reference because it is a U.S. patent that published and issued on July 29, 1997. Osterberg (Ex.1030) qualifies as a 102(b) reference because it is a printed publication that published in August 1999. This combination of references was not considered by the examiner during examination.

2. Ground 2: Claims 61-67 are obvious in view of Drucker ’600 (Ex. 1028) and further in view of Kornfelt (Ex. 1027), Osterberg (Ex. 1030), and Holthuis (Ex. 1005).

Similarly, each reference applied in Ground 2 is prior art under 35 U.S.C. § 102(b) because each was published more than one year prior to the earliest effective filing date of the ’886 patent, which is December 29, 2000. Drucker ’600 (Ex. 1028) qualifies as a 102(b) reference because it is a printed publication that published on November 26, 1998. Holthuis (Ex. 1005) qualifies as a 102(b) reference because it is a U.S. patent that published and issued on March 5, 1996.

Kornfelt, and Osterberg are 102(b) references as described above. This combination of references was not considered by the examiner during examination.

3. Ground 3: Claims 51 and 75 are obvious in view of Drucker '379 and further in view of Kornfelt, Osterberg, and Munroe.

See below regarding Ground 4.

4. Ground 4: Claim 68 is obvious in view of Drucker '600 and further in view of Kornfelt, Osterberg, Holthuis, and Munroe.

Similarly, each reference applied in Ground 3 and Ground 4 is prior art under 35 U.S.C. § 102(b) because each was published more than one year prior to the earliest effective filing date of the '886 patent, which is December 29, 2000. Munroe (Ex.1022) qualifies as a 102(b) reference because it is a printed publication that published in 1999. Drucker '379, Drucker '600, Holthuis, Kornfelt, and Osterberg are 102(b) references as described above. This combination of references was not considered by the examiner during examination.

B. A Person of Ordinary Skill in the Art

A person of ordinary skill in the art is a pharmaceutical scientist having an advanced degree (a Master's or a Ph.D.) or equivalent experience in pharmaceutics, pharmaceutical formulations or the pharmaceutical arts with knowledge of formulating peptide formulations and the clinical application of therapeutics in treating gastrointestinal disorders. (Ex. 1001 ¶ 22).

C. Claims 46-52 and 61-75 are Obvious

The prior art references cited herein when combined disclose all of the limitations of the claims at issue. A person of ordinary skill in the art would recognize this and have had a reason to combine these prior art disclosures with a reasonable expectation of success in arriving at the claimed subject matter. Furthermore, Petitioner is not aware of any evidence of secondary considerations of non-obviousness and the Applicant provided none during patent prosecution. To the extent Patentee alleges commercial success to rebut the obviousness of claims 46- 52 and 69-75, no nexus between these claims and any alleged commercial success exists.

1. Grounds 1 and 3: All of the limitation of Claims 46-52, and 69-75 are disclosed in the combination of the cited references

Claims 46 and 52 are independent claims directed to GLP-2 formulations. Claims 47 to 50 are dependent on claim 46 and further describe the GLP-2 formulation. Claim 69 is an independent claim directed to a method of treatment using a GLP-2 formulation. Claims 70-74 are dependent on claim 69 and further describe the GLP-2 formulation and administration of the GLP-2 formulation.

Regarding independent claims 46 and 52, Drucker ’379 discloses the same GLP-2 peptide formulations as set forth in both of these claims (Ex.1029 at 3:23-27, 9:43-47, and 13:8-33; Ex. 1001 at ¶¶ 50, 52, 57-59, and 78-88). L-histidine set

forth in (c) of claims 46 and 52 as well as mannitol in (d) of these same claims (sucrose is included under (d) in claim 52), were very well known and widely used for stabilization of peptide formulations, including glucagon as disclosed by Kornfelt and Osterberg (Ex. 1027 at 2:20-53 and 2:65-67; Ex. 1001 at ¶¶ 60-64, 90-92, and 95). In fact, Osterberg discloses L-histidine as a protein stabilizer in formulations containing sucrose (Ex. 1030 at 307 (4. Conclusions) and 305 (3.3 Freeze Drying); Ex. 1001 at ¶¶61 and 100). Kornfelt teaches the L-histidine as a stabilizing amino acid is useful across a very broad range of pH levels (from pH 1-7) (Ex.1027 at 3:9-11; Ex. 1001 at ¶¶ 73 and 101). Osterberg specifically teaches that both L-Histidine and sucrose are useful at the physiologically acceptable pH levels claimed in the ’886 patent (Ex.1030 at 305; Ex. 1001 at¶¶ 73 and 101).

The specific amounts referred to in claim 46 for GLP-2, L- histidine, and mannitol are disclosed in Drucker ’379 and Kornfelt.

Claim 46 requires “about 0.1 to about 50 mg/ml of a GLP-2 peptide or an analog thereof” (Ex. 1003). About 0.1 to about 50 mg/ml of a GLP-2 peptide or an analog thereof is disclosed in Drucker ’379 when it states “[t]he results presented herein below demonstrate that a dose of GLP-2 peptide equivalent to about 100 μg/kg (or less) administered twice daily over 10 days can generate very significant increases in small bowel mass” (Ex. 1029 at 11:22-26; Ex. 1001 at ¶53). It was known to a person of ordinary skill in the art that a dosage given in μg/kg can be

converted to mg/ml based upon selection of a volume for administration of a dose of the formulation (Ex. 1001 at ¶53). For an average human weighing 70 kg (154 lbs.), a dose of 100 μg/kg as disclosed in Drucker '379 in 1 ml of formulation (a typical amount for liquid formulations) is calculated as follows: 100μg/kg x 70 kg/ml x 1 g/1000000 μg x 1000 mg/1 g = 7 mg/ml. 7 mg/ml falls within the range of about 0.1 to about 50 mg/ml. (*Id.*). Furthermore, Drucker '379 discloses a formulation of a GLP-2 analog at 130 mg/l in phosphate buffered saline (PBS) which is equivalent to 0.13 mg/ml, also falling within the range specified by the claim (Ex.1029 at 13:27-33; Ex. 1001 at¶ 54).

Claim 46 recites "about 0.5 to about 1% L-histidine" (Ex.1003). Kornfelt discloses an amount of stabilizing amino acid of 0.01 to 50 micromoles per mg glucagon (Ex. 1027 at 2:65-67; Ex. 1001 at ¶ 62.). To convert an amount of L-histidine in micromoles per mg glucagon as disclosed in Kornfelt to a percentage of L-histidine expressed as weight/volume of formulated product prior to lyophilization in gms/ml (x 100) as specified in the claim requires a dosage of glucagon in mg per ml formulation. Assuming a dosage of 1.1 mg glucagon/ml formulation as disclosed in Kornfelt (Ex. 1027 at 3:50-4:45), 50 μmol L-histidine/mg glucagon x 1.1 mg glucagon/ml formulation x 1 mol L-histidine/1000000 μmol L-histidine x 155 g L-histidine/mol L-histidine x 100 is

equal to 0.85% histidine (Ex. 1001 at ¶ 63).This amount is within the range specified by the claim (Ex. 1001 at ¶ 64).

Claim 46 requires about 2% to about 5% mannitol (Ex.1003). Kornfelt teaches that "[t]he excipient is preferably present in an amount of from 10 to 600 micromoles per mg glucagon giving an optimum stabilization" (Ex. 1027 at 2:58-60; Ex. 1001 at ¶ 65). To convert an amount of mannitol in micromoles per mg glucagon as disclosed in Kornfelt to a percentage of mannitol expressed as weight/volume of formulated product prior to lyophilization in gms/ml (x 100) as specified in the claim requires a dosage of glucagon in mg per ml formulation. Assuming a dosage of 1.1 mg glucagon/ml formulation as disclosed in Kornfelt (Ex. 1027 at 3:50-4:45), the following equation converts micromoles/mg to a %: 10-600 μmol mannitol/mg glucagon x 1.1 mg glucagon/ml formulation x 1 mol mannitol/1000000 μmol mannitol x 182 g mannitol/mol mannitol x 100 resulting in 0.2-12% mannitol which includes the range within the claim (Ex. 1001 at ¶ 66).

Dependent claims 47-50 incorporate every limitation of claim 46 and recite further limitations on the GLP-2 formulation. Drucker '379 discloses the limitations of claim 47 by stating that a GLP-2 formulation can include h(Gly2)GLP-2((Ex. 1029 at 6:52-55; Ex. 1001 at ¶144). Drucker '379 also discloses the limitations of claim 48 by describing a GLP-2 analog in lyophilized form (Ex. 1029 at 10:25-33; Ex. 1001 at ¶ 146). Lyophilization was very well

known and widely used for stabilization of protein drug formulations as disclosed in Osterberg (Ex.1030 at 301; Ex. 1001 at ¶ 146). Similarly, Kornfelt discloses lyophilized formulations of the related peptide glucagon (Ex. 1027 at 2:20-50 and 3:13-18; Ex. 1001 at ¶ 146). Drucker '379 further discloses a GLP-2 formulation meeting the pH limitations of claims 49 and 50 (Ex. 1029 at 9:43-51 and 13:8-26; Ex. 1001 at ¶¶148-149).

All of the limitations of independent claim 69 are disclosed in Drucker '379, Osterberg and Kornfelt. For example, Drucker '379 discloses administering a GLP-2 formulation with a therapeutically effective amount of GLP-2 analog to treat gastrointestinal disease (Ex. 1029 at 3:33-39; Ex. 1001 at ¶¶110-115). As described above with respect to claims 46 and 52, Drucker '379, Osterberg and Kornfelt disclose a GLP-2 formulation having the limitations set forth in in the claim (Ex.1029 at 9:43-47 and 13:8-26; Ex. 1027 at 2:20-53 and 65-67; Ex. 1030 at 307;Ex. 1001 at ¶¶ 116-130). Regarding the "enhancing, maintaining, or promoting the growth or functioning of the gastrointestinal tract" limitation, Drucker '379 discloses the GLP-2 analogs in its formulations have intestinal tissue growth promoting properties and specifically promote growth of small bowel tissue (Ex. 1029 at 1:12-15, 2:15-19, 3:28-32, and 10:38-40; Ex. 1001 at ¶ 133).

Dependent claims 70-74 incorporate every limitation of claim 69. Nevertheless, Drucker '379 discloses a GLP-2 formulation meeting the pH

limitations of claims 70 and 71 (Ex. 1029 at 9:43-51 and 13:8-26; Ex. 1001 at ¶¶ 148-149). Drucker '379 additionally discloses its GLP-2 formulation containing the GLP-2 analog specified in claim 72 (Ex. 1029 at 4:7-24; Ex. 1001 at ¶ 144). Drucker '379 also discloses GLP-2 formulations administered by injection or infusion as set forth in claims 73 and 74(Ex. 1029 at 9:43-51 and 13:8-33; Ex. 1001 at ¶¶ 153-154).

With regard to Ground 3, the combination of Drucker '379, Kornfelt, Osterberg, and Munroe disclose all of the elements of claims 51 and 75. Claims 51 and 75 are directed to a "GLP-2 analog has one or more amino acid substitutions, additions, deletions, or modifications and has GLP-2 receptor binding activity." (Ex.1003). Drucker '379 discloses a GLP-2 formulation containing the GLP-2 analog specified in claim 51 and 75 (Ex.1029 at 6:52-55; Ex, 1001 at ¶ 151). Such analogs have intestinotrophic activity (Ex. 1029 at 15:1-35; Ex, 1001 at ¶ 151). Further, Munroe specifically teaches the GLP-2 analog disclosed in Drucker '379, [Gly2] GLP-2, has GLP-2 receptor binding activity(Ex.1022 at Table 2 at 1573; Ex. 1001 at ¶ 151).

Based on these disclosures, the combination of Drucker '379, Kornfelt, Osterberg, and Munroe discloses all of the limitations of claims 46-52, and 69-75. The following claim charts show the limitations of claims 46-52, and 69-75 and the disclosure of each limitation in the prior art.

Claims 46-50	Ground 1: Claims 46-50 are obvious in view of Drucker '379, Kornfelt, and Osterberg
46. A GLP-2 formulation comprising:	Drucker '379 describes a GLP-2 formulation: "In another of its aspects, the invention provides a pharmaceutical composition comprising a GLP-2 analog of the present invention in a therapeutically effective amount, and preferably in an intestinotrophic amount, and a pharmaceutically acceptable carrier" (Ex. 1029 at 3:23-27).
(a) about 0.1 to about 50 mg/ml of a GLP-2 peptide or an analog thereof;	Drucker '379 teaches this limitation: "In another of its aspects, the invention provides a pharmaceutical composition comprising a GLP-2 analog of the present invention in a therapeutically effective amount, and preferably in an intestinotrophic amount, and a pharmaceutically acceptable carrier" (Ex. 1029 at 3:23-27). "The results presented herein below demonstrate that a dose of GLP-2 peptide equivalent to about 100 μg/kg (or less) administered twice daily over 10 days can generate very significant increases in small bowel mass (Ex. 1029 at 11:22-26; *see* Ex. 1001 at ¶ 53 for conversion). "EXAMPLE 2 GLP-2 Analog Formulation The GLP-2 analogs were formulated for injection . . . in phosphate buffered saline . . . The GLP-2 analog, as a powdered peptide, is added to the working PBS solution as required to generate formulations having the desired peptide concentrations. For example, to generate a PBS solution of GLP-2 analog at 130 mg/l, 5.2 mg of GLP-2 analog is dissolved in 40 ml of PBS to yield a GLP-2 concentration of 130 μg/ml, 0.5 ml is injected twice daily" (Ex. 1029 at 13:8-33; *see* Ex. 1001 at ¶ 54 for conversion).
(b) a phosphate	Drucker '379 teaches this limitation:

buffer in an amount sufficient to adjust the pH of the formulation to a pharmaceutically tolerable level;	"In one embodiment of the invention, the compounds are…utilized as aqueous solutions in sterile and pyrogen-free form and optionally buffered to physiologically tolerable pH, e.g., a slightly acidic or physiological pH. Thus, the compounds may be administered in a vehicle such as distilled water or, more desirably, in saline, phosphate buffered saline or 5% dextrose solution" (Ex. 1029 at 9:43-54). "EXAMPLE 2 GLP-2 Analog Formulation The GLP-2 analogs were formulated for injection . . . in phosphate buffered saline . . . . For the PBS-formulated GLP-2 analog preparations, a 10X stock PBS solution was first prepared, using 80 g NaCl (BDH ACS 783), 2 g KCl (BDH ACS 645), 11.5 g Na_2 HPO_4 (Anachemia AC-8460), and 2 g KH_2 PO_4 (Malinckrodt AR7100), which was brought to a total volume of one liter with sterile distilled water. The final working solution was obtained by 10:1 dilution of the stock solution with sterile distilled water and adjusted to pH 7.3-7.4 if necessary, using sufficient volumes of 10N Na OH. The working solution was then autoclaved for 30 minutes. In the final working PBS solution, concentrations were 137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2 HPO_4.7H2O, and 1.4 mM KH_2 PO_4" (Ex. 1029 at 13:8-26).
(c) about 0.5 to about 1% L-histidine; and	Kornfelt teaches this limitation: "The invention relates to a stabilized pharmaceutical preparation comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte, especially an amino acid or dipeptide or a mixture thereof and optionally an excipient . . . . "A pharmaceutically acceptable ampholyte to be used in accordance with the invention may be selected from the group consisting of amino acids or derivations thereof such as . . . histidine . . . .

	"An amino acid to be used in accordance with the present invention is preferably a naturally occurring alpha amino acid. Such amino acids may be 1 or d amino acids or a mixture thereof" (Ex. 1027 at 2:20-42). "In order to obtain the desired stabilization, the stabilizing amino acid . . . may be present in an amount from 0.01 to 50 micromoles per mg glucagon" (Ex. 1027 at 2:65-67; *see* Ex. 1001 at ¶ 63 for conversion). Osterberg discloses: "L-histidine may be regarded as a multifunctional protein "stabilizer . . . ." (Ex. 1030 at 307 (4. Conclusions)). "Freeze drying of L-histidine from solutions having a pH in the range 4-8 showed that L-histidine has a rather low tendency to crystallize during freeze drying . . . ." (Ex. 1030 at 305 (3.3 Freeze Drying)).
(d) about 2 to about 5% mannitol.	Kornfelt discloses a glucagon formulation with about 2 to about 5% mannitol: "The invention relates to a stabilized pharmaceutical preparation comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte, especially an amino acid or dipeptide or a mixture thereof and optionally an excipient . . . . "An excipient may be selected from…sugar alcohols…such as mannitol . . . ." (Ex. 1027 at 2:20-53). "The excipient is preferably present in an amount of from 10 to 600 micromoles per mg glucagon giving an optimum stabilization" (Ex. 1027 at 2:58-60; *see* Ex. 1001 at ¶ 65 for conversion.)
47. The GLP-2 formulation of claim 46, wherein the GLP-2 is h(Gly2)GLP-2.	Drucker '379 teaches the GLP-2 is h(Gly2)GLP-2: "In specific embodiments of the invention, there are provided the following Ala^2-substituted GLP-2 analogs: . . . $[Gly^2]$hGLP-2 . . . ." (Ex. 1029 at 6:52-55).

48. The GLP-2 formulation of claim 47, wherein the formulation is lyophilized.	Drucker '379 discloses a GLP-2 formulation that is lyophilized: "The GLP-2 analog can be utilized in the form of a sterile-filled vial or ampoule . . . the vial or ampoule may contain the GLP-2 peptide in a form, such as a lyophilized form, suitable for reconstitution in a suitable carrier, such as phosphate-buffered saline" (Ex. 1029 at 10:25-33). Kornfelt discloses a glucagon formulation that is lyophilized: A pharmaceutical preparation of the invention in lyophilized form preferably also comprises an excipient, e.g. for facilitating the lyophilization and rapid and complete redissolution thereof when reconstituting the preparation before use" (Ex. 1027 at 2:20-50). "The invention also relates to a method for the preparation of a pharmaceutical preparation comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte wherein glucagon is dissolved in a solution of the ampholyte and optional excipient and lyophilized, optionally after sterile filtration" (Ex. 1027 at 3:13-18). Osterberg discloses protein formulations are generally lyophilized: "Protein drugs are generally chemically and physically unstable in solution and freeze-drying is frequently used to obtain an acceptable shelf life . . . ." (Ex.1030 at 301).
49. The GLP-2 formulation of claim 47, wherein the pH of the formulation is selected from the group consisting of greater than about 6.0, and from about 6.9 to about 7.9.	Drucker '379 teaches this limitation: "In one embodiment of the invention, the compounds are . . . utilized as aqueous solutions in sterile and pyrogen-free form and optionally buffered to physiologically tolerable pH, e.g., a slightly acidic or physiological pH" (Ex. 1029 at 9:43-51). "EXAMPLE 2

	GLP-2 Analog Formulation The GLP-2 analogs were formulated for injection . . . in phosphate buffered saline . . . . For the PBS-formulated GLP-2 analog preparations, a 10X stock PBS solution was first prepared, using 80 g NaCl (BDH ACS 783), 2 g KCl (BDH ACS 645), 11.5 g Na_2 HPO_4 (Anachemia AC-8460), and 2 g KH_2 PO_4 (Malinckrodt AR7100), which was brought to a total volume of one liter with sterile distilled water. The final working solution was obtained by 10:1 dilution of the stock solution with sterile distilled water and adjusted to pH 7.3-7.4 if necessary, using sufficient volumes of 10N Na OH. The working solution was then autoclaved for 30 minutes. In the final working PBS solution, concentrations were 137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2 HPO_4.7H2O, and 1.4 mM KH_2 PO_4" (Ex. 1029 at 13:8-26).
50. The GLP-2 formulation of claim 49, wherein the pH of the formulation is from about 7.3 to about 7.4.	*See* Claim 49; *N.B.* Example 2 (Ex. 1029 at 13:8-26).

Claim 52	**Ground 1: Claim 52 is obvious over Drucker '379, Kornfelt, and Osterberg**
52. A GLP-2 formulation comprising:	*See* Claim 46.
(a) a medically useful amount of a naturally occurring GLP-2 peptide or an analog thereof;	*See* Claim 46(a)
(b) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a	*See* Claim 46(b)

physiologically tolerable level;	
(c) L-histidine in an amount sufficient to stabilize the formulation; and	*See* Claim 46(c)
(d) a bulking agent selected from the group consisting of mannitol and sucrose.	Kornfelt teaches mannitol or sucrose in a glucagon formulation: "The invention relates to a stabilized pharmaceutical preparation comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte, especially an amino acid or dipeptide or a mixture thereof and optionally an excipient . . . . "An excipient may be selected from disaccharides such as . . . sucrose, [and] sugar alcohols such . . . mannitol . . . " (Ex. 1027 at 2:20-53). Osterberg discloses: "[T]he addition of sucrose abolished the crystallization of L-histidine. The reduced tendency for crystallization of L-histidine is very important in the formulation design . . . ." (Ex. 1030 at 304).

Claims 69-74	**Ground 1: Claims 69-74 are obvious in view of Drucker '379, Kornfelt, and Osterberg**
69. A method for treating a human or animal having a gastrointestinal disorder, disease or condition for which treatment with GLP-2 is indicated, the	Drucker '379 describes such a method: "Besides promoting bowel growth, in another of its aspects the invention provides a method for treating a gastrointestinal disease by administering to a patient suffering from gastrointestinal disease a therapeutically effective amount of a GLP-2 analog of the invention, together with a pharmaceutically acceptable carrier, in

method comprising the step of administering a therapeutically effective amount of a GLP-2 formulation comprising:	order to reduce a pathological effect or symptom of the gastrointestinal disease" (Ex. 1029 at 3:33-39).
(a) a GLP-2 peptide or an analog thereof;	Drucker '379 teaches a GLP-2 peptide or an analog thereof: "Besides promoting bowel growth, in another of its aspects the invention provides a method for treating a gastrointestinal disease by administering to a patient suffering from gastrointestinal disease a therapeutically effective amount of a GLP-2 analog of the invention, together with a pharmaceutically acceptable carrier, in order to reduce a pathological effect or symptom of the gastrointestinal disease" (Ex. 1029 at 3:33-39).
(b) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a pharmaceutically tolerable level;	*See* Claim 46(b) and Claim 52(b).
(c) L-histidine; and	*See* Claim 46(c) and Claim 52(c).
(d) a bulking agent selected from the group consisting of mannitol and sucrose,	*See* Claim 46(d) and Claim 52(d). Osterberg discloses: "[T]he addition of sucrose abolished the crystallization of L-histidine. The reduced tendency for crystallization of L-histidine is very important in the formulation design . . . ." (Ex. 1030 at 304).
thereby enhancing, maintaining, or promoting the growth or	Drucker '379 teaches enhancing, maintaining, or promoting the growth or functioning of the gastrointestinal tract:

functioning of the gastrointestinal tract.	"This invention relates to glucagon-related peptides having intestinal tissue growth promoting properties, and to their use therapeutically to treat various medical conditions resulting from the impaired growth or loss of such tissue" (Ex. 1029 at 1:12-15). "There have now been discovered analogs of GLP-2 which promote growth of small bowel tissue. It is accordingly a general object of the present invention to provide such GLP-2 analogs and to provide for their use therapeutically and for related purposes" (Ex. 1029 at 2:15-19). "In a further aspect, the invention provides a method for promoting growth of small bowel tissue in a patient in need thereof, comprising the step of delivering to the patient an intestinotropic amount of a GLP-2 analog of the present invention" (Ex. 1029 at 3:28-32). "According to the present invention, the GLP-2 analog is administered to treat patients that would benefit from growth of small bowel tissue" (Ex. 1029 at 10:38-40).
70. The method of claim 69, wherein the pH of the GLP-2 formulation is selected from the group consisting of greater than about 5.5, greater than about 6.0, and from about 6.9 to about 7.9.	*See* Claim 49
71. The method of claim 70, wherein the pH of the formulation is from about 7.3 to about 7.4.	*See* Claims 49 and 50; *N.B.* Example 2 (Ex. 1029 at 13:8-26).
72. The method of	Drucker '379 teaches the GLP-2 peptide is h(Gly2)GLP-2:

claim 70, wherein the GLP-2 peptide is h(Gly2)GLP-2.	"In specific embodiments of the invention, there are provided the following Ala^2-substituted GLP-2 analogs: . . . [Gly2]hGLP-2 . . . ." (Ex. 1029 at 6:52-55).
73. The method of claim 69, wherein the GLP-2 formulation is administered by injection.	Drucker '379 teaches the GLP-2 formulation is administered by injection: "In one embodiment of the invention, the compounds are formulated for administration . . . by injection, e.g., sub-cutaneously, intramuscularly or intravenously . . . ." (Ex. 1029 at 9:43-51). "EXAMPLE 2 GLP-2 Analog Formulation The GLP-2 analogs were formulated for injection . . . The GLP-2 analog, as a powdered peptide, is added to the working PBS solution as required to generate formulations having the desired peptide concentrations. For example, to generate a PBS solution of GLP-2 analog at 130 mg/l, 5.2 mg of GLP-2 analog is dissolved in 40 ml of PBS to yield a GLP-2 concentration of 130 μg/ml, 0.5 ml is injected twice daily" (Ex. 1029 at 13:8-33).
74. The method of claim 69, wherein the GLP-2 formulation is administered by infusion.	Drucker '379 teaches the GLP-2 formulation is administered by infusion: "In one embodiment of the invention, the compounds are formulated for administration by infusion . . . ." (Ex. 1029 at 9:43-51).

Claims 51 and 75	**Ground 3: Claims 51 and 75 are obvious in view of Drucker '379, Kornfelt, Osterberg, and Munroe**
51. The GLP-2 formulation of claim 46, wherein said GLP-2 analog has one or more amino	Drucker '379 teaches the GLP-2 analog has one or more amino acid substitutions, additions, deletions, or modifications: "In addition to exhibiting intestinotrophic activity . . . , the

acid substitutions, additions, deletions, or modifications and has GLP-2 receptor binding activity.	GLP-2 analogs of the present invention incorporate an amino acid substitution at one or more sites within a GLP-2 peptide 'background' . . . Thus, the present peptides incorporate an amino acid substitution in the context of any mammalian GLP-2 species . . . ." (Ex. 1029 at 4:7-24). Munroe teaches [Gly-2]Glp-2 binds to the GLP-2 receptor and has intestinotrophic activity (Ex.1022 at Table 2 at 1573).
75. The method of claim 69, wherein said GLP-2 analog has one or more amino acid substitutions, additions, deletions, or modifications and has GLP-2 receptor binding activity.	*See* claim 51.

2. Grounds 2 and 4: The limitations of Claims 61-68 directed to a Kit are disclosed in the combination of the prior art references

Claim 61 is an independent claim directed to a kit comprising a lyophilized GLP-2 formulation. Claims 62-68 are dependent on claim 61 and further describe the lyophilized GLP-2 formulation and the kit.

All of the limitations of independent claim 61 were known in art. In fact, lyophilization was very well known and widely used for stabilization of protein drug formulations as disclosed in Osterberg (Ex. 1030 at 301; Ex. 1001 at ¶ 161). Drucker '600 discloses a kit containing GLP-2 or a GLP-2 analog in lyophilized form (Ex. 1028 at 21:26-30; Ex. 1001 at ¶¶ 161-162). Drucker '600 also discloses

a lyophilized GLP-2 formulation having the phosphate buffer limitation (ii) (Ex. 1028 at 19:25-36, 21:26-30, and 45:35-46:13; Ex. 1001 at ¶¶ 164-167). L-histidine of limitation (iii) and mannitol, and sucrose of limitation (iv) were very well known and widely used for stabilization of peptide formulations, such as glucagon (Ex. 1027 at 2:20-50; Ex. 1001 at¶ 169). For example, Osterberg discloses L-histidine as a protein stabilizer, and further discloses the use of L-histidine in combination with sucrose meeting the L-histidine limitation (iii) and the mannitol or sucrose limitation (iv) (Ex. 1030 at307 (4. Conclusions) and 305 (3.3 Freeze Drying); Ex. 1001 at ¶ 169).

In regard to the vial of sterile water at limitation (b), it was known in the art to reconstitute lyophilized peptide formulations with a suitable diluent. This is demonstrated by Kornfelt reconstituting lyophilized formulations of the related peptide glucagon with a suitable diluent including sterile water (Ex. 1027 at 1:19-22 and 3:55-67; Ex. 1001 at ¶¶ 178-179). Drucker ’600 discloses the use of distilled water for administration of its GLP-2 formulations (Ex. 1028 at 19:25-36; Ex. 1001 at ¶ 178). Holthuis specifically describes a kit with a vial of water (Ex.1005 at 5:28-34; Ex. 1001 at ¶ 185).

Regarding the instructions limitation (c), it was known in the art to provide instructions directing reconstitution of lyophilized peptide formulations in a kit. The FDA requires labeling instructions for reconstitution for every drug product.

(21 C.F.R. 201 *et seq.*; Ex. 1001 at ¶ 182). This is supported by Drucker '600 discloses package (i.e., a kit) for its lyophilized GLP-2 or GLP-2 analog including a label instructing use (Ex. 1028 at 21:15-30; Ex. 1001 at ¶ 182).

Dependent claims 62-68 incorporate every limitation of claim 61 and require the additional limitations of the lyophilized GLP-2 formulation and kit. All of these limitations, are disclosed in the prior art. For example, Drucker '600 discloses that a lyophilized GLP-2 formulation meets the pH limitations of claims 62 and 63 (Ex. 1028 at 19:25-33 and 45:35-46:13 ; Ex. 1001 at ¶¶ 194-196). Drucker '600 discloses a lyophilized GLP-2 formulation can include h(Gly2)GLP-2 of claim 64 (Ex. 1028 at 31:5-11; Ex. 1001 at ¶ 197). Drucker '600 also discloses that lyophilized GLP-2 formulations can be administered by injection as required by claim 65 (Ex. 1028 at 19:25-33; Ex. 1001 at ¶ 200). Clearly, it was known in the art to use an injection device in a kit for administration of injectable lyophilized peptide formulations after reconstitution. Holthuis specifically describes a kit with an injection device (Ex.1005 at 5:34-36; Ex. 1001 at ¶ 209).

Kornfelt discloses reconstituted formulations of the related peptide glucagon containing histidine meeting the stability limitations required by claims 66 and 67 (Ex. 1027 at 3:50-5:15; Ex. 1001 at ¶ 202). Kornfelt determined stability of the lyophilized glucagon formulation by reconstituting a lyophilized formulation, heating to 60° C, and then looking for purity of the peak of glucagon by reverse

phase HPLC over a 4 week period (Ex. 1027 at 4:45-50; Ex. 1001 at ¶ 202). The results show that a formulation of glucagon containing 20mM histidine retained 90% of glucagon over the 4 week period (Ex. 1027 at 4:55-5:15; Ex. 1001 at ¶ 202).

For Ground 4, Drucker '600 discloses a lyophilized GLP-2 formulation containing the GLP-2 analog required in claim 68 (Ex. 1028 at 31:5-11 and 30:30-31:1; Ex. 1001 at ¶¶ 203-205). Further, it was known that an analog described in Drucker '600, [Gly2]GLP-2, has activity and GLP-2 receptor binding activity (Ex.1022 at 1573, Table 2; Ex. 1001 at ¶ 205).

The combination of Drucker '600, Kornfelt, Osterberg, Holthuis, and Munroe discloses every limitation of claims 61-68.The following claim chart shows the limitations of claims 61-68 and the prior art addressing each limitation.

Claims 61-67	**Ground 2: claim 61-67 are obvious in view of Drucker '600, Kornfelt, Osterberg, and Holthuis**
61. A kit comprising:	Drucker '600 discloses a kit: "the invention provides kits . . . ." (Ex. 1028 at 7:29-30). "For use in stimulating growth of the upper gastrointestinal tract, and/or enhancing upper gastrointestinal tract functioning in a mammal including a human, the present invention provides in one of its aspects a package, in the form of a sterile-filled vial or ampoule, that contains a tissue growth promoting amount of the GLP-2 or GLP-2 analog, in either unit dose or multi-dose amounts, wherein the package incorporates a label instructing use of its contents for the promotion of such growth" (Ex. 1028 at

	21:15-23).
(a) a lyophilized GLP-2 formulation comprising:	Drucker '600 discloses a lyophilized GLP-2 formulation: "Alternatively, and according to another embodiment of the invention, the package provides the GLP-2 or GLP-2 analog in a form, such as a lyophilized form, suitable for reconstitution in a suitable carrier, such as phosphate-buffered saline" (Ex. 1028 at 21:26-30). Kornfelt discloses a glucagon formulation that is lyophilized: A pharmaceutical preparation of the invention in lyophilized form preferably also comprises an excipient, e.g. for facilitating the lyophilization and rapid and complete redissolution thereof when reconstituting the preparation before use" (Ex. 1027 at 2:20-50). "The invention also relates to a method for the preparation of a pharmaceutical preparation comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte wherein glucagon is dissolved in a solution of the ampholyte and optional excipient and lyophilized, optionally after sterile filtration" (Ex. 1027 at 3:13-18). Osterberg discloses protein formulations are generally lyophilized: "Protein drugs are generally chemically and physically unstable in solution and freeze-drying is frequently used to obtain an acceptable shelf life . . . ." (Ex. 1030 at 301).
(i) a GLP-2 peptide or an analog thereof;	Drucker '600 discloses this limitation: "Alternatively, and according to another embodiment of the invention, the package provides the GLP-2 or GLP-2 analog in a form, such as a lyophilized form, suitable for reconstitution in a suitable carrier, such as phosphate-buffered saline." (Ex. 1028 at 21:26-30).
(ii) a phosphate buffer in an amount	Drucker '600 discloses this limitation:

sufficient to adjust the pH of the formulation to a pharmaceutically acceptable level;	"[T]he compounds are formulated . . . and optionally buffered to physiologically tolerable pH, *e.g.*, a slightly acidic or physiological pH. Thus, the compounds may be administered in a vehicle such as distilled water, or more desirably, in saline, phosphate buffered saline, or 5% dextrose solution" (Ex. 1028 at 19:25-36). "Alternatively, and according to another embodiment of the invention, the package provides the GLP-2 or GLP-2 analog in a form, such as a lyophilized form, suitable for reconstitution in a suitable carrier, such as phosphate-buffered saline" (Ex. 1028 at 21:26-30). "GLP-2 Administration 50.4 mg h[Gly2]GLP-2 (ALX-0600) obtained from Allelix on August 1, 1997 dissolved in sterile H_2O; 5N NaOH was used to pH the solution to a final pH 7. This batch of peptide was used for all experiments. Aliquots of 0.2, 0.5, 1.0, 2.0 mg/ml were frozen at -80° C. 600 μg of h[Gly2]-GLP-2 in 1 ml solution was aliquoted into 399 ml phosphate buffer saline (PBS - 137 mM NaCl, 2.7 mM KCl, 4.3 mM $Na_2HPO_4 \cdot 7H_2O$, 1.4 mM KH_2PO_4, pH 7.3) to obtain a final concentration of 1.5 ug/mL . . . ." (Ex. 1028 at 45:35-46:13).
(iii) L-histidine; and	Kornfelt discloses a lyophilized glucagon formulation with L-histidine: "The invention relates to a stabilized pharmaceutical preparation comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte, especially an amino acid or dipeptide or a mixture thereof and optionally an excipient . . . . "A pharmaceutically acceptable ampholyte to be used in accordance with the invention may be selected from the group consisting of amino acids or derivations thereof such . . . histidine . . . . "An amino acid to be used in accordance with the

	present invention is preferably a naturally occurring alpha amino acid. Such amino acids may be l or d amino acids or a mixture thereof . . . . "A pharmaceutical preparation of the invention in lyophilized form preferably also comprises an excipient, e.g. for facilitating the lyophilization and rapid and complete redissolution thereof when reconstituting the preparation before use" (Ex. 1027 at 2:20-50). Osterberg discloses: "L-histidine may be regarded as a multifunctional protein stabilizer . . . ." (Ex. 1030 at 307 (4. Conclusions)). "Freeze drying of L-histidine from solutions having a pH in the range 4-8 showed that L-histidine has a rather low tendency to crystallize during freeze drying . . . ." (Ex. 1030 at 305, (3.3 Freeze Drying)).
(iv) a bulking agent selected from the group consisting of mannitol and sucrose;	Kornfelt discloses a lyophilized glucagon formulation with mannitol or sucrose: "A pharmaceutical preparation of the invention in lyophilized form preferably also comprises an excipient, e.g. for facilitating the lyophilization and rapid and complete redissolution thereof when reconstituting the preparation before use. "An excipient may be selected from disaccharides such as … sucrose, [and] sugar alcohols such . . . mannitol . . . ." (Ex. 1027 at 2:45-53). Osterberg discloses: "[T]he addition of sucrose abolished the crystallization of L-histidine. The reduced tendency for crystallization of L-histidine is very important in the formulation design . . . ." (Ex. 1030 at 304).
(b) a vial of sterile water for reconstitution; and	Drucker '600 discloses distilled water as a vehicle for administration of its GLP-2 formulations:

	"In one embodiment of the invention, the compounds are . . . utilized as aqueous solutions in sterile and pyrogen-free form and optionally buffered to physiologically tolerable pH, *e.g.,* a slightly acidic or physiological pH. Thus, the compounds may be administered in a vehicle such as distilled water or, more desirably, in saline, phosphate buffered saline or 5% dextrose solution" (Ex. 1028 at 19:25-36). Kornfelt discloses: "Glucagon is at present marketed in the form of a lyophilized product for injection comprising lactose as the sole excipient. The lyophilisate is to be reconstituted using a suitable diluent" (Ex. 1027 at 1:19-22). Holthius discloses: "[T]here is provided a medically useful kit, comprising at least one vial containing a freeze-dried PTH preparation of the invention, at least one vial containing sterile water for reconstitution of the preparation, and a sheet of instructions directing reconstitution of the freeze-dried PTH" (Ex. 1031 at 5:28-34).
(c) instructions directing reconstitution.	Drucker '600 teaches: "For use in stimulating growth of the upper gastrointestinal tract, and/or enhancing upper gastrointestinal tract functioning in a mammal including a human, the present invention provides in one of its aspects a package, in the form of a sterile-filled vial or ampoule, that contains a tissue growth promoting amount of the GLP-2 or GLP-2 analog, in either unit dose or multi-dose amounts, wherein the package incorporates a label instructing use of its contents for the promotion of such growth . . . . Alternatively, and according to another embodiment of the invention, the package provides the GLP-2 or GLP-2 analog in a form, such as a lyophilized form, suitable for reconstitution in a suitable carrier, such as phosphate-buffered saline" (Ex. 1028 at 21:15-30).

62. The kit of claim 61, wherein the pH of the GLP-2 formulation is selected from the group consisting of greater than about 5.5, greater than about 6.0, and from about 6.9 to about 7.9.	Drucker '600 teaches the pH of the GLP-2 formulation is selected from the group consisting of greater than about 5.5, greater than about 6.0, and from about 6.9 to about 7.9 by disclosing: "[T]he compounds are formulated for administration by infusion or by injection . . . and are accordingly utilized as aqueous solutions in sterile and pyrogen-free form and optionally buffered to physiologically tolerable pH, *e.g.*, a slightly acidic or physiological pH" (Ex. 1028 at 19:25-33). "GLP-2 Administration 50.4 mg h[Gly^2]GLP-2 (ALX-0600) obtained from Allelix on August 1, 1997 dissolved in sterile H_2O; 5N NaOH was used to pH the solution to a final pH 7. This batch of peptide was used for all experiments. Aliquots of 0.2, 0.5, 1.0, 2.0 mg/ml were frozen at -80° C. 600 μg of h[Gly2]-GLP-2 in 1 ml solution was aliquoted into 399 ml phosphate buffer saline (PBS - 137 mM NaCl, 2.7 mM KCl, 4.3 mM $Na_2HPO_4 \cdot 7H_2O$, 1.4 mM KH_2PO_4, pH 7.3) to obtain a final concentration of 1.5 ug/mL . . . ." (Ex. 1028 at 45:35-46:13).
63. The kit of claim 62, wherein the pH of the formulation is from about 7.3 to about 7.4.	Drucker '600 teaches a GLP-2 formulation in which the pH of the formulation is from about 7.3 to about 7.4: *See* Claim 62.
64. The kit of claim 63, wherein the GLP-2 peptide is h(Gly2)GLP-2.	Drucker '600 discloses the GLP-2 peptide is h(Gly2)GLP-2 when it describes the GLP-2 analog [Gly-2] human (Gly^2) GLP-2: "The GLP-2 analogs are suitably analogs of either human GLP-2 (human [Gly^2] GLP-2) or rat GLP-2 (rGLP-2). In a preferred embodiment of the invention, rat or human GLP-2 is altered at position 2 to confer DPP-IV resistance by substituting a Gly for an Ala. Human GLP-2 having Gly substituted for Ala at position 2 is referenced herein as [Gly 2] human [Gly^2] GLP-2" (Ex. 1028 at 31:5-11).
65. A kit of claim 61, further comprising	Drucker '600 discloses "the compounds are formulated for administration . . . by injection, *e.g.*, sub-cutaneously,

an injection device for administration.	intramuscularly or intravenously . . . .” (Ex. 1028 at 19:25-33). Holthius discloses an injection device for administration of its reconstituted parathyroid hormone (PTH) preparations in a kit: “The kit may further comprise an injection device for administration of the reconstituted formulation by the end-user” (Ex. 1031 at 5:34-36).
66. The kit of claim 61, wherein following reconstitution the GLP-2 formulation is stable for at least about 12 hours.	Kornfelt teaches the stability of formulations of glucagon containing histidine reconstituted from lyophilized form for at least 12 hours: EXAMPLE 1 Preparation of formulations comprising glucagon, lactose and an amino acid or a dipeptide. In an analogous manner as described above formulations were prepared from glucagon, lactose and an amino acid or a dipeptide. As reference was used a formulation comprising glucagon and lactose prepared as described above. Formulations having the following compositions per vial were prepared: **Reference:** Glucagon 1.1 mg Lactose USP/Ph Eur 107 mg 1N HCl ad pH 2.8 **Test formulations:** Glucagon 1.1 mg Lactose USP/Ph Eur 107 mg Ampholyte 5, 10, 20 mM HCl/NaOH ad pH 2.8

The ampholytes tested were:

Formulation	
A1	Glycine
A2	Glycylglycine
A3	Histidine
A4	Aspartic acid
A5	Glutamic acid
A6	Leucine
A7	Alanine
A8	Asparagine
A9	Valine

The test formulations were incubated at 60° C., for a total period of 4 weeks. The degradation of the formulations were measured weekly by reverse phase HPLC. The results are shown in Table 1 and FIGS. 1-9.

The results show that a very pronounced stabilization of glucagon is obtained by adding stabilizing agent in accordance with the invention.

TABLE 1

Week	Conc. AA (mM)	Glycine RPC %	Glycylglycine RPC %	Histidine RPC %	Reference RPC %
0	5	98.00	97.90	97.90	97.60
	10	97.90	97.90	98.00	
	20	97.80	97.90	97.90	
1	5	97.10	96.40	94.70	55.80
	10	92.40	97.00	97.20	
	20	93.40	96.10	94.00	
2	5	91.60	95.20	91.20	29.30
	10	94.50	93.70	94.40	
	20	91.60	90.80	90.90	

	TABLE 1-continued Week / Conc. AA (mM) / Glycine RPC % / Glycylglycine RPC % / Histidine RPC % / Reference RPC % 3 / 5 / 94.80 / 95.30 / 88.10 / 25.30 10 / 93.20 / 94.30 / 87.60 20 / 91.80 / 93.60 / 94.10 4 / 5 / 84.60 / 91.70 / 90.90 / 26.90 10 / 93.30 / 87.50 / 93.30 20 / 85.40 / 90.10 / 94.20 (Ex. 1027 at 3:50-5:15).
67. The kit of claim 61, wherein following reconstitution the GLP-2 formulation is stable for up to about 24 hours.	Kornfelt teaches the stability of formulations of glucagon containing histidine reconstituted from lyophilized form for at least 24 hours. *See* claim 66.

Claim 68	**Ground 4: Claim 68 is obvious in view of Drucker '600, Kornfelt, Osterberg, Holthuis, and Munroe**
68. The kit of claim 61, wherein said GLP-2 analog has one or more amino acid substitutions, additions, deletions, or modifications, and has GLP-2 receptor binding activity.	Drucker '600 teaches the GLP-2 analog has one or more amino acid substitutions, additions, deletions, or modifications: "The GLP-2 analogs are suitably analogs of either human GLP-2 (human [Gly^2] GLP-2) or rat GLP-2 (rGLP-2) . In a preferred embodiment of the invention, rat or human GLP-2 is altered at position 2 to confer DPP- IV resistance by substituting a Gly for an Ala. Human GLP-2 having Gly substituted for Ala at position 2 is referenced herein as [Gly 2] human [Gly^2] GLP-2" (Ex. 1028 at 31:5-11). Drucker '600 teaches: "[A]ny substitution, addition or deletion of GLP-2 that does not destroy the activity of GLP-2 may be usefully employed in this invention. In preferred embodiments the GLP-2 analogs are at least as [active] as native human

	GLP-2. In the most preferred embodiments, the GLP-2 analog has enhanced activity compared with native human GLP-2. For example, such analogs may exhibit enhanced serum stability, enhanced receptor binding and enhanced signal transducing activity" (Ex. 1028 at 30:30-31:1). Munroe teaches [Gly-2]Glp-2 binds to the GLP-2 receptor and has intestinotrophic activity (Ex.1022 at 1573, Table 2).

D. There is a Reason to Combine the Cited References

A person of ordinary skill in the art would have been motivated to combine these prior art references in order to form a stable GLP-2 formulation for therapeutic use because there was a known design need and because GLP-2 is structurally similar to glucagon of the prior art. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 420 (2007). The claimed GLP-2 formulation, methods, and kits are nothing more than a combination of known ingredients for a predictable result of stability as confirmed by routine testing. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

A design need for formulating a stable GLP-2 formulation for therapeutic use would be recognized by a person of ordinary skill in the art based on FDA requirements (Ex. 1024 at 8; Ex. 1001 at ¶¶ 68, 102, 140, and 193). For example, Osterberg describes that it was known that formulations of peptides in some cases lack storage stability. (Ex. 1030 at 301; Ex. 1001 at ¶¶ 68, 102, 40, and 193).

Similarly, Kornfelt recognizes a storage stability problem that occurs with glucagon formulations (Ex. 1027 at 1:23-30; Ex. 1001 at ¶¶ 68, 102, 40, and 193).

A solution to this storage stability problem is to formulate glucagon with L-histidine as a stabilizing amino acid, and an excipient or bulking agent such as sucrose or mannitol as described by Kornfelt (Ex.1027 at 5:1-15; Ex. 1001 at ¶¶ 69, 103, 141, and 194). The pH of the storage stable formulations of glucagon disclosed in Kornfelt can range from 1-7 (Ex. 1027 at 3:9-11; Ex. 1001 at ¶¶ 73, 103, 141, and 194). As a result, one of ordinary skill in the art would certainly recognize that the same storage stable formulation can be applied to molecules structurally similar to glucagon like GLP-2.

In fact, Osterberg supports using this combination in formulations by disclosing that the addition of sucrose to L-histidine "abolished the crystallization of L-histidine" and that "[t]he reduced tendency for crystallization of L-histidine is very important in the formulation design, . . . " (Ex.1030 at 304; Ex. 1001 at ¶¶ 73, 103, 141, and 194). Osterberg also discloses that it was known that L-histidine and sucrose provide stable formulations over a range of pH values from 4-8 (Ex. 1030 at 305 (3.3 Freeze Drying"); Ex. 1001 at ¶¶ 73, 103, 141, and 194). Based on these disclosures, one of ordinary skill in the art would have looked to Kornfelt and/or Osterberg to solve the design need for storage stable formulations for GLP-2 and its analogs (Ex. 1001 at ¶¶ 69, 103 , 141, and 194).

Indeed, a person of ordinary skill in the art looking to formulate a stable formulation of GLP-2, would also be motivated to use the same methods of stabilizing glucagon because glucagon and GLP-2 are closely related proteins sharing many of the same properties (Ex. 1001 at ¶¶ 71, 105, 144, and 196). For example, GLP-2 was known to be a peptide hormone member of the glucagon superfamily (Ex. 1018 at 879; Ex. 1001 at ¶¶ 71, 105, 143, and 196). GLP-2 was also known to share amino acid sequence similarity of at least 50% to that of glucagon and have a similar molecular weight (Ex. 1018 at 879, Fig. 3; Ex. 1001 at ¶¶ 71, 105, 143, and 196). Furthermore, GLP-2 and glucagon share an alpha helix region as a secondary structural feature (Ex. 1019 at 254, Table V; Ex. 1025 at 3:1-11; Ex. 1001 at ¶¶ 71, 105, 143, and 196). Analogs of GLP-2 with receptor binding activity possess an alpha helix despite having sequence changes (Ex.1020 at 8888 (Abstract); Ex. 1001 at ¶¶ 71, 105, 143, and 196). Despite the Patentee arguing otherwise during prosecution, there was no evidence that amino acid sequence differences between glucagon and GLP-2 affect the presence of the alpha helix structure of the peptides (Ex. 1020 at 888, Abstract; Ex. 1001 ¶¶ 71, 105, 143, and 196). Because of these similarities, a person of ordinary skill in the art would know that they could equally apply the solution for creating storage stable formulations of glucagon to formulating stable GLP-2 formulations with long term storage capabilities (Ex. 1001 at ¶¶ 71, 105, 143, and 196).

With regard to kits containing lyophilized formulations of pharmaceutical compositions of GLP-2 or analogs for therapeutic use, they were also known. For example, Drucker ’600 teaches a kit including a lyophilized formulation of GLP-2 or GLP-2 analog and a desired carrier, as well as a label with instructions for use (Ex. 1028 at 21:15-30; Ex. 1001 at ¶¶166-173 and 188-191). The same publication teaches that the carrier can be sterile water and that the pharmaceutical composition can be formulated for injection (Ex. 1028 at 19:25-33; Ex. 1001 at ¶¶183-186 and 208). A person of ordinary skill in the art reading Drucker ’600 would easily prepare a kit with a vial of sterile water, an injection device, and instruction for use as taught by Holthuis (Ex.1005 at 5:28-36; Ex. 1001 at ¶¶ 208-209).

One of ordinary skill in the art would have a reason to combine Drucker ’379 or Drucker ’600 with Kornfelt, Osterberg , and Munroe to arrive at the claims at issue. This combination of disclosures in the prior art provides a solution to form a storage stable GLP-2 formulation for therapeutic use as well as well-known prior art components in the form of a kit to allow the ease of use of GLP-2.

E. There is a Reasonable Expectation of Success

A person of ordinary skill in the art would have a reasonable expectation of success in formulating GLP-2 in combination with L-histidine and sucrose or

mannitol to create a storage stable formulation in view of the combination of references cited in this petition for IPR.

The cited prior art provides guidance for preparing storage stable formulations for peptides such as glucagon. Through routine experimentation, a person of ordinary skill in the art would easily substitute active ingredients having similar physio-chemical profiles to glucagon to form stable formulations as taught by Kornfelt (Ex. 1001 at ¶¶ 74, 107, 145, and 195). As discussed above, GLP-2 and glucagon are structurally similar (Ex. 1001 at ¶¶ 71, 107, 143, and 196).

Kornfelt evidences that one of ordinary skill in the art would have success because it shows that using L-histidine and mannitol or sucrose forms storage stable formulations of glucagon even after being reconstituted and heat stressed (Ex.1027 at 3:50-5:15; Ex. 1001 at ¶¶ 73, 106, 144, and 197). Osterberg shows that it was well-known that sugar and amino acids, including sucrose and L-histidine, were added to formulations to prevent inactivation during freezing and to stabilize proteins in long term storage (Ex.1030 at 5:28-36; Ex. 1001 at ¶¶ 73, 106, 144, and 197). In fact, Kornfelt teaches that lyophilized formulations of glucagon, when reconstituted, heated to 60° C and stored for 4 weeks, retain 90% of glucagon (Ex. 1027 at 3:50-5:15; Ex. 1001 at ¶¶ 73, 106, 144, and 197).

Kornfelt also teaches that storage stable glucagon formulations have a pH range of 1-7 (Ex.1027 at 3:9-11; Ex. 1001 at ¶¶ 73, 106, 144, and 197). Therefore,

despite any arguments the Patentee made during prosecution regarding the difference in the solubility of glucagon at pH 2-4 as compared to GLP-2 at pH 5.5, there is no evidence that this difference would impact the reasonable expectation of success in obtaining a storage stable formulation of GLP-2 (Ex. 1001 at ¶¶ 73, 106, 144, and 197). In fact, Osterberg describes that formulations containing L-histidine and sucrose are storage stable over the pH range of 4-8 (Ex.1030 at 304 (Figure 4); Ex. 1001 at ¶¶ 73, 106, 144, and 197). Because it was known that L-histidine and sucrose provide stable formulations for peptides over a range of pHs, any difference in solubility of glucagon at a lower pH does not affect the reasonable expectation of success that a storage stable formulation of GLP-2 using L-histidine and sucrose could be formed at a physiological or slightly acidic pH (Ex. 1001 at ¶¶ 73, 106, 144, and 197). This is particularly true given that absolute certainty is not required to demonstrate a reasonable expectation of success. *See Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d. 1186 (Fed. Cir. 2014).

At the very least, the L-histidine stabilized formulation taught by Kornfelt would be obvious to try with GLP-2 or analog thereof. Kornfelt and Osterberg teach that preparing stable formulations do not involve numerous parameters. Kornfelt provides specific guidance as to a small number of known options, such as L-histidine and sucrose or mannitol , for preparing a storage stable formulation of glucagon (Ex. 1001 at ¶¶ 74, 107, 145, and 198). Kornfelt also provides a

detailed methodology for preparing formulations of glucagon with L-histidine as a stabilizing amino acid and an excipient like lactose or mannitol (Ex. 1001 at ¶¶ 74, 107, 145, and 198).This detailed methodology establishes that formulating peptides, like glucagon, is nothing more than the routine application of a well-known laboratory methods using ingredients having known properties to arrive at the claims at issue. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

The same holds true with regard to the kit in the claims at issue. Packaging a lyophilized formulation in a vial containing sterile water and including an injection device as well as instructions for use does not impact the reasonable expectation of success as formulations of such kits were known and standard in the art (Ex. 1001 at ¶¶ 185, 190, and 208).

F. There is No Evidence of Secondary Considerations

The Patentee cannot argue unexpected results. During examination, when the claims at issue were rejected as being obvious, the Patentee failed to rebut the Examiner's rejection with any evidence of unexpected results. Rather, the Patentee merely argued that there was no motivation to combine (Ex.1016 at 16-17).

Furthermore, any attempt to now argue that the results are unexpected is non-persuasive in view of the results presented in Kornfelt (Ex. 1027 at 3:50-5:15; Ex. 1001 at ¶¶ 75, 108, 146, and 199). Kornfelt demonstrates that the stability of reconstituted lyophilized glucagon under heat stress is 90% or greater over a 4

week period (Ex. 1027 at 3:50-5:15; Ex. 1001 at ¶¶ 75, 146, 108, and 199). The results presented in the '886 patent for storage stability of GLP-2 are similar. (Ex. 1001 at ¶¶ 75, 108, 146, and 199). For example, the '886 patent discloses the stability of reconstituted lyophilized GLP-2 for 4 hours after heating to 60° C (Ex. 1003 at 8:1-50) and claims stabilities of at least 12 or 24 hours. It is on this basis that the Patentee cannot establish any unexpected results. Differences in stability in the '886 patent are a difference in degree rather than kind, which is contrary to unexpected results that require a difference in kind rather than degree. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013).

In view of the publications discussed above and the Patentee's failure to provide any evidence of unexpected results, the claimed subject matter represents nothing more than the predictable use of known components having known function, and represents a strong case for obviousness that overcomes any evidence of secondary considerations. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

Moreover, any evidence of secondary considerations must show a nexus to the claimed invention. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013). To the extent Patentee alleges commercial success to rebut the obviousness of claims 46- 52 and 69-75, no nexus between these claims and any alleged commercial success exists. What's more, any feature providing the basis

for the alleged secondary considerations must be due to the merits of the claimed invention beyond what is known in the prior art. *Id.* at 739. That is not the case here. The only limitations allegedly imparting patentability of these claims are the addition of L-histidine and sucrose or mannitol to the GLP-2 formulations. These limitations, however, were known in the art as exemplified by Kornfelt and Osterberg and cannot provide the nexus to the secondary considerations (Ex. 1001 at ¶¶ 76, 109, 147, and 200).

Thus, Petitioner submits that claims 46-52 and 61-75 are obvious in view of the references cited herein.

VII. CONCLUSION

For at least the reasons given above, claims 46-52 and 61-75 of the '886 patent are unpatentable because they are obvious over the prior art.

Because Petitioner has shown the claims to be unpatentable, Petitioner has also shown a likelihood of success on the merits, and this petition should be granted and requests that the PTAB institute an *Inter Partes* Review of claims 46-52 and 61-75 on the grounds of obviousness set forth above.

Respectfully submitted,

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on the 1st day of April, 2015, a complete and entire copy of this Petition for *Inter Partes* Review Under 37 C.F.R. §42.100, alongside an accompanying Power of Attorney, Appendix of Exhibits, and Exhibits 1001-1030, were provided via electronic mail and UPS, postage prepaid, to the Patent Owner by serving the correspondence address of record for the '886 patent.

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