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☒ a final action under 37 C.F.R. §1.113;

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Dated: July 27, 2016

Respectfully submitted,
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First Named Inventor/Applicant Name:	Stephen Comiskey
Filer:	Anne Elizabeth Fleckenstein/Sandra Laramore
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(54) **Title**: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

(57) **Abstract**: The invention provides low-dose formulations of guanylate cyclase-C ("GCC") agonist peptides and methods for their use. The formulations of the invention can be administered either alone or in combination with one or more additional therapeutic agents, preferably an inhibitor of cGMP-dependent phosphodiesterase or a laxative.

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FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

RELATED APPLICATIONS

[01] This application claims priority to U.S. Patent Application No. 13/421,769 filed on March 15, 2012, the content of which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[02] The present invention relates to low-dose formulations of guanylate cyclase C peptide agonists useful for the treatment and prevention of various diseases and disorders.

BACKGROUND OF THE INVENTION

[03] Guanylate cyclase C is a transmembrane form of guanylate cyclase that is expressed on various cells, including gastrointestinal epithelial cells (reviewed in Vaandrager 2002 *Mol. Cell. Biochem.* 230:73-83). It was originally discovered as the intestinal receptor for the heat-stable toxin (ST) peptides secreted by enteric bacteria and which cause diarrhea. The ST peptides share a similar primary amino acid structure with two peptides isolated from intestinal mucosa and urine, guanylin and uroguanylin (Currie, *et al.*, *Proc. Nat'l Acad. Sci. USA 89*:947-951 (1992); Hamra, *et al.*, *Proc. Nat'l Acad. Sci. USA 90*:10464-10468 (1993); Forte, L., *Reg. Pept. 81*:25-39 (1999); Schulz, *et al.*, *Cell 63*:941-948 (1990); Guba, *et al.*, *Gastroenterology 111*:1558-1568 (1996); Joo, *et al.*, *Am. J. Physiol. 274*:G633-G644 (1998)).

[04] In the intestines, guanylin and uroguanylin act as regulators of fluid and electrolyte balance. In response to high oral salt intake, these peptides are released into the intestinal lumen where they bind to guanylate cyclase C localized on the luminal membrane of enterocytes (simple columnar epithelial cells of the small intestines and colon). The binding of the guanylin peptides to guanylate cyclase C induces electrolyte and water excretion into the intestinal lumen via a complex intracellular signaling cascade that is initiated by an increase in cyclic guanosine monophosphate (cGMP).

[05] The cGMP-mediated signaling that is initiated by the guanylin peptides is critical for the normal functioning of the gut. Any abnormality in this process could lead to gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel diseases. Inflammatory bowel disease is a general name given to a group of disorders that cause the intestines to become inflamed, characterized by red and swollen tissue. Examples include ulcerative colitis and Crohn's disease. Crohn's disease is a serious inflammatory disease that predominantly affects the ileum and colon, but can also occur in other sections of the gastrointestinal tract. Ulcerative colitis is exclusively an inflammatory disease of the colon, the large intestine. Unlike Crohn's disease, in which all layers of the intestine are involved, and in which there can be normal healthy bowel in between patches of diseased bowel, ulcerative colitis affects only the innermost lining (mucosa) of the colon in a continuous manner. Depending on which portion of the gastrointestinal tract is involved, Crohn's disease may be referred to as ileitis, regional enteritis, colitis, etc. Crohn's disease and ulcerative colitis differ from spastic colon or irritable bowel syndrome, which are motility disorders of the gastrointestinal tract. Gastrointestinal inflammation can be a chronic condition. It is estimated that as many as 1,000,000 Americans are afflicted with inflammatory bowel disease, with male and female patients appearing to be equally affected. Most cases are diagnosed before age 30, but the disease can occur in the sixth, seventh, and later decades of life.

[06] IBS and chronic idiopathic constipation are pathological conditions that can cause a great deal of intestinal discomfort and distress but unlike the inflammatory bowel diseases, IBS does not cause the serious inflammation or changes in bowel tissue and it is not thought to increase the risk of colorectal cancer. In the past, inflammatory bowel disease, celiac disease and IBS were regarded as completely separate disorders. Now, with the description of inflammation, albeit low-grade, in IBS, and of symptom overlap between IBS and celiac disease, this contention has come under question. Acute bacterial gastroenteritis is the strongest risk factor identified to date for the subsequent development of postinfective irritable bowel syndrome. Clinical risk factors include prolonged acute illness and the absence of vomiting. A genetically determined susceptibility to inflammatory stimuli may also be a risk factor for irritable bowel syndrome. The underlying pathophysiology indicates increased intestinal permeability and low-grade inflammation, as well as altered motility and visceral sensitivity. Serotonin (5-hydroxytryptamine [5-HT]) is a key modulator of gut

function and is known to play a major role in pathophysiology of IBS. The activity of 5-HT is regulated by cGMP.

[07] While the precise causes of IBS and inflammatory bowel diseases (IBD) are not known, a disruption in the process of continual renewal of the gastrointestinal mucosa may contribute to disease pathology in IBD and aggravate IBS. The renewal process of the gastrointestinal lining is an efficient and dynamic process involving the continual proliferation and replenishment of unwanted damaged cells. Proliferation rates of cells lining the gastrointestinal mucosa are very high, second only to the hematopoietic system. Gastrointestinal homeostasis depends on both the proliferation and programmed cellular death (apoptosis) of epithelial cells lining the gut mucosa. Cells are continually lost from the villus into the lumen of the gut and are replenished at a substantially equal rate by the proliferation of cells in the crypts, followed by their upward movement to the villus. The rates of cell proliferation and apoptosis in the gut epithelium can be increased or decreased in a variety of circumstances, *e.g.*, in response to physiological stimuli such as aging, inflammatory signals, hormones, peptides, growth factors, chemicals and dietary habits. In addition, an enhanced proliferation rate is frequently associated with a reduction in turnover time and an expansion of the proliferative zone. The proliferation index is much higher in pathological states such as ulcerative colitis and other gastrointestinal disorders. Intestinal hyperplasia is a major promoter of gastrointestinal inflammation. Apoptosis and cell proliferation together regulate cell number and determine the proliferation index. Reduced rates of apoptosis are often associated with abnormal growth, inflammation, and neoplastic transformation. Thus, both increased proliferation and/or reduced cell death may increase the proliferation index of intestinal tissue, which may in turn lead to gastrointestinal inflammatory diseases.

[08] In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of gastrointestinal mucosa by maintaining the balance between proliferation and apoptosis. For example, uroguanylin and guanylin peptides appear to promote apoptosis by controlling cellular ion flux. Given the prevalence of inflammatory conditions in Western societies a need exists to improve the treatment options for inflammatory conditions, particularly of the gastrointestinal tract.

[09] Peptide agonists of guanylate cyclase C agonists ("GCC agonists") are described in U.S. Patent Nos. 7,041,786, 7,799,897, and U.S. Patent Application Publication Nos. US2009/0048175, US 2010/0069306, US 2010/0120694, US 2010/0093635, and US 2010/0221329. However, the formulation of peptides for pharmaceutical delivery presents a number of special problems. For example, peptides are subject to structural modifications by a variety of degradation mechanisms resulting in problems of chemical and physical instability of the formulation.

SUMMARY OF THE INVENTION

[10] The present invention provides low-dose formulations of peptide agonists of guanylate cyclase C ("GCC") and methods for their use in the treatment and prevention of human diseases and disorders, such as a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction; Crohn's disease, ulcerative colitis, inflammatory bowel disease, colonic pseudo-obstruction, obesity, congestive heart failure, and benign prostatic hyperplasia. In certain embodiments, the formulations are stabilized against chemical degradation of the peptide. The low-dose formulations of the invention have unexpected efficacy in humans in a dosage range that was not predicted based on studies in primates. The formulations of the invention are particularly useful for the treatment or prevention of chronic idiopathic constipation. In certain embodiments, the GCC agonists are analogs of uroguanylin and bacterial ST peptides. In preferred embodiments, the analogs have superior properties compared to the naturally occurring or "wild-type" peptides. Examples of such superior properties include a high resistance to degradation at the N-terminus and C-terminus from carboxypeptidases, aminopeptidases, and/or by other proteolytic enzymes present in the stimulated human intestinal juices and human gastric juices. Examples of GCC agonists that can be used in the formulations and methods of the invention are described in more detail below and in U.S. Patent Nos. 7,041,786, 7,799,897, and U.S. Patent Application Publication Nos. US2009/0048175, US 2010/0069306, US 2010/0120694, US 2010/0093635, and US 2010/0221329, each of which is incorporated herein by reference in its entirety.

[11] The invention provides an oral dosage formulation comprising one or more pharmaceutically acceptable excipients and at least one GCC agonist peptide, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249. In one embodiment, the GCC agonist peptide has a chromatographic purity of no less than 90%, no less than 90.5%, no less than 91%, no less than 92%, no less than 93%, no less than 94%, no less than 95%, no less than 96%, no less than 97%, no less than 98%, or no less than 99%. The chromatographic purity of the GCC agonist peptide is determined as area percent by HPLC. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1 and 9. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 8 and 9. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg or 9.5 mg.

[12] In one embodiment, the GCC agonist peptide has a total impurity content of no greater than 10%, no greater than 9.5%, no greater than 9%, no greater than 8%, no greater than 7%, no greater than 6%, no greater than 5%, no greater than 4%, no greater than 3%, no greater than 2%, or no greater than 1%. The total impurity content is determined as total area percentages of impurities by HPLC. The impurities do not include any pharmaceutically acceptable excipient used for the formulation. In one embodiment, the formulation is substantially free of inorganic acids and carboxylic acids, e.g., HCl, phosphoric acid, or acetic acid. In this context, carboxylic acids do not include amino acids or peptides. In this context "substantially" free of acids means that the acid content of the formulation at the time of packaging is preferably less than 0.2%, less than 0.1%, less than 0.05%, less than 0.01%, less than 0.005%, or less than 0.001% of the total weight of the formulation. In one embodiment, the formulation is free of HCl.

[13] In one embodiment, the formulation is a solid formulation. In one embodiment, the formulation is in the form of a powder, granule, sachet, troche, tablet, or capsule. In another embodiment, the formulation is a liquid formulation and the GCC agonist peptide is in solution or suspension in a lipophilic liquid. In one embodiment, the liquid is a refined specialty oil or a medium chain triglyceride or related ester. In one embodiment, the refined specialty oil is selected from Arachis oil, Castor oil, cottonseed oil, maize (corn) oil, olive oil,

sesame oil, soybean oil, and sunflower oil. In one embodiment, the medium chain triglyceride or related ester is AKOMED E, AKOMED R, CAPTEX 355, LABRAFAC CC, LABRAFAC PG, LAUROGLYCOL FCC, MIGLYOL 810, MIGLYOL 812, MIGLYOL 829, MIGLYOL 840, and SOFTISAN 645. In one embodiment, the liquid is selected from the group consisting of medium chain triglycerides, propylene glycol dicaprylocaprate, vitamin E, soybean oil, Cremaphor, PG, and PG 400. In one embodiment, the unit dose is a powder, tablet, or capsule. In one embodiment, the unit dose is a liquid-filled capsule. In one embodiment, the capsule or tablet is in a blister pack or strip. Preferably, the blister pack or strip is made of a material that is impermeable to water vapor and oxygen. In one embodiment the blister pack is comprised of a metal foil. In one embodiment the blister pack is a FOIL/FOIL blister pack. In one embodiment, the container of the blister pack is flushed with an inert gas such as nitrogen or argon. In one embodiment, the container further includes a desiccant. In a preferred embodiment the desiccant is a molecular sieve. In one embodiment, the unit dose is in a high density polyethylene bottle having a seal. In one embodiment, the bottle further comprises a desiccant. In one embodiment, the bottle further comprises an oxygen scavenger or molecular sieve. In one embodiment, the bottle is nearly impermeable to oxygen and water vapor (e.g., much more impermeable than a HDPE bottle), such as an OxyGuard bottle.

[14] In one embodiment, the one or more pharmaceutically acceptable excipients include an inert carrier. In one embodiment, the inert carrier is a selected from mannitol, lactose, a microcrystalline cellulose, or starch. In one embodiment, the inert carrier has a particle size of from 50 to 900 microns, from 50 to 800 microns, from 50 to 300 microns, from 50 to 200 microns, from 75 to 150 microns, from 75 to 200 microns, or from 75 to 300 microns.

[15] In one embodiment, the GCC agonist peptide is stabilized against chemical or physical degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

[16] In one embodiment, the one or more pharmaceutically acceptable excipients include a divalent cation salt such as calcium chloride. In one embodiment, the one or more pharmaceutically acceptable excipients comprise an amino acid, such as leucine, histidine, or arginine, or an amine such TRIS or TRIS/HCl.

[17] In one embodiment, the oral dosage formulation consists of the GCC agonist peptide described herein, an inert carrier (e.g., Celphere SCP-100, Avicel PH 102, or Avicel PH 112), and a lubricant (e.g., magnesium stearate). In one embodiment, the formulation consists of the GCC agonist peptide, an inert carrier (e.g., Avicel PH 200), a divalent cation salt (e.g., calcium chloride or calcium ascorbate), an amino acid (e.g., leucine, histidine, or arginine) or a protective amine (e.g., TRIS), a coating agent (e.g., Methocel ES Premium LV) and optionally a lubricant (e.g., magnesium stearate) or another additive (e.g., trehalose). In one embodiment, the formulation consists of the GCC agonist peptide, a binder (e.g., Provsolv SMCC 90 LM), and a disintegrant (e.g., Explotab). In one embodiment, the formulation consists of the GCC agonist peptide, a diluent (e.g., Mannogem EZ), a binder (e.g., Provsolv SMCC 90 LM), a disintegrant (e.g., Explotab), a lubricant (e.g., Pruv).

[18] The invention also provides a process for making the oral dosage formulations described herein, wherein the process comprises a step of dry granulation, wet granulation, or spray coating followed by drying. In another embodiment, the process comprises a step of dry mixing. In a preferred embodiment the step of dry mixing includes geometric blending. In one embodiment, the process comprises a step of direct compression. In one embodiment, the process for making the oral dosage formulations described herein is a spray coating-drying process which includes (a) providing an aqueous solution comprising: a GCC agonist peptide selected from the group consisting of SEQ ID NOs: 1-54 and 56-249, and one or more pharmaceutically acceptable excipients, wherein the concentration of the GCC agonist peptide ranges from 10 to 60 mg/mL; and (b) applying the aqueous solution to a pharmaceutically acceptable carrier to generate a GCC agonist peptide-coated carrier.

[19] In one embodiment of the spray coating-drying process above, the one or more pharmaceutically acceptable excipients comprise a divalent cation salt wherein the divalent cation is selected from Ca^{2+}, Mg^{2+}, Zn^{2+}, and Mn^{2+}. In one embodiment, the one or more pharmaceutically acceptable excipients comprise an amino acid selected from leucine, isoleucine, and valine. In one embodiment, the one or more pharmaceutically acceptable excipients comprise a coating agent (such as hypromellose Methocel E5 PremLV). In one embodiment, the aqueous solution has a pH greater than 4 (e.g., 4.5-5.5, 5-6, about 5, or greater than 5) or even greater than 7. In one embodiment, the aqueous solution is substantially free of inorganic acids and carboxylic acids. In one embodiment, the GCC

agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, and 56. In one embodiment, the process further includes drying the GCC agonist peptide-coated carrier.

[20] The invention further provides an oral dosage formulation made by the process described herein. Preferably, the GCC agonist peptide as made is stabilized against chemical or physical degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

[21] The invention also provides a method for treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject an oral dosage formulation comprising at least one GCC agonist peptide, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249. Preferably, the subject is a human subject. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1 and 9. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg, 9.5 mg, or 10 mg.

[22] In one embodiment, the disease or disorder is a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, constipation, gastroparesis, heartburn, gastric cancer, and H. pylori infection. In a preferred embodiment, the gastrointestinal disease or disorder is chronic idiopathic constipation.

[23] In one embodiment, the method further comprises administering to the subject an effective amount of an inhibitor of a cGMP-specific phosphodiesterase. In one embodiment, the cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone, vardenifil, and suldenifil.

[24] In one embodiment, the method further comprises administering to the subject an effective amount of at least one laxative. In one embodiment, the at least one laxative is selected from the group consisting of SENNA, MIRALAX, PEG, or calcium polycarbophil.

[25] In one embodiment, the method further comprises administering to the subject an effective amount of at least one anti-inflammatory agent.

[26] The invention also provides pharmaceutical compositions comprising the formulations described herein.

[27] Other features and advantages of the invention will be apparent from and are encompassed by the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[28] Figure 1: Plecanatide (SP-304) treatment reduced time to first BM following daily dose.

[29] Figure 2: Effect of daily treatment with plecanatide on spontaneous bowel movements (SBM) in chronic constipation patients.

[30] Figure 3: Effect of daily treatment with plecanatide on complete spontaneous bowel movements (CSBM) in chronic constipation patients.

[31] Figure 4: Effect of daily treatment with plecanatide on Bristol Stool Form Scores (BSFS) in chronic constipation patients.

[32] Figure 5: Effect of daily treatment with plecanatide on straining scores in chronic constipation patients

[33] Figure 6: Percentage of subjects reporting improvements in abdominal discomfort scores after 14-days of daily treatment with plecanatide.

DETAILED DESCRIPTION

[34] The invention provides pharmaceutical formulations of peptide GCC agonists. It is intended that the formulations of the invention are "pharmaceutical" formulations, meaning that they are suitable for pharmaceutical use. Accordingly, the term "formulations" as used herein is meant to encompass pharmaceutical formulations even if "pharmaceutical" is not expressly stated. Pharmaceutical compositions comprising the formulations described herein

are also provided by the invention. The formulations of the invention preferably provide stability against chemical and physical degradation of the peptide, e.g., plecanatide (i.e., SEQ ID #1).

[35] The invention is based in part upon the discovery that mannitol mixes very effectively with the GCC agonist peptides described herein and provides stability against degradation, allowing the peptides to be formulated at very low doses. The invention is also based in part on the discovery that very low doses of the GCC agonist peptides described herein are effective for the treatment of diseases and disorders in humans. The dosage range found to be effective was not predicted based on animal studies. The invention is also based in part upon the discovery that a divalent cation (e.g., Ca^{2+}) and/or an amino acid (e.g., leucine or arginine) stabilize the GCC agonist peptides described herein during a process (e.g., spray coating-drying process) of manufacturing a formulation of the GCC agonist peptides and provides stability against degradation both during the manufacturing process and storage of the formulation.

[36] Plecanatide is a charged peptide due to the presence of four carboxylic acids and single amine group with a calculated pKa of approximately 3.5. Therefore plecanatide is likely to interact with ions in solution or in the solid state. Plecanatide is a hygroscopic peptide requiring the control of water during manufacture and storage to promote long term stability. Plecanatide is prone to degradation by oxidation in the presence of residual peroxides or formaldehyde contaminants that are formed from peroxide reaction with polymeric excipients. The present invention discloses a manufacturing process and dry solid formulation compositions that minimizes water content. The formulations are comprised of components to minimize levels of residual formaldehyde and peroxides commonly found in many pharmaceutical excipients. The invention also discloses additives (i.e. $CaCl_2$) that may function as local desiccants in the formulation. Divalent cation salts such as calcium ascorbate, $MgCl_2$, $ZnCl_2$, $MnCl_2$ and $CaCl_2$ bind plecanatide and sterically hinder reactive species such as water or oxygen from causing plecanatide degradation by molecular displacement. The invention further includes scavengers of residual formaldehyde (amines such as TRIS or TRIS/HCl or amino acids such as leucine, isoleucine and valine), and discloses packaging confirmations to minimize oxygen exposure and water vapor during storage. The invention also discloses a stable manufacturing process comprised of initially

dissolving plecanatide in cold water to minimize solution degradation, followed by spray coating the peptide solution on particles and drying to remove moisture.

[37] The formulations of the invention are particularly useful for the treatment or prevention of a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, chronic idiopathic constipation, gastroparesis, heartburn, gastric cancer, and H. pylori infection.

[38] In one embodiment, the formulations of the invention are used in a method for the treatment of constipation. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining. Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics. In a preferred embodiment, the constipation is chronic idiopathic constipation.

[39] The stabilized formulations of the invention comprise at least one GCC agonist peptide formulated with one or more excipients such that the peptide is stabilized against chemical degradation. Chemical degradation of peptides results from a number of mechanisms including oxidation, water-mediated degradation, and reaction with aldehydes or reducing sugars. The ideal excipient or combination of excipients will be non-hygroscopic, have few or no reducing sugars, and be substantially free of contaminants such as iron, peroxide, and formaldehyde. The formulations of the invention are preferably substantially free of water. In this context “substantially” free of water means that the water content of the formulation at the time of packaging is preferably less than 7%, less than 5%, less than 1%, or less than 0.5% of the total weight of the formulation. In one embodiment the amount of

water is between 0.1 to 5% of the total weight of the formulation. In one embodiment, the amount of water in the formulation of the invention manuafactured through a spray-coating process is less than 0.5% (e.g., about 0.47%).

[40] In the context of the present formulations, the term "stable" or "stabilized" refers to the resistance of the peptide to chemical or physical degradation over time. Preferably, a stable formulation of the invention retains an amount of the peptide in the formulation over a period of time that is at least 90%, preferably at least 95%, and most preferably at least 99% the amount of peptide initially present in the formulation. In one embodiment, a stable formulation of the invention, over a period of time (e.g., 18 month), has an increase in the total impurity content not greater than 8%, not greater than 7%, not greater than 6%, not greater than 5%, not greater than 4%, not greater than 3%, not greater than 2%, or not greater than 1%. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 18 months, at least 20 months, or at least 24 months when stored at 25 degrees Celsius (25C) and 60 % relative humidity. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 18 months, at least 20 months, or at least 24 months when stored at 2-8 degrees Celsius (2-8C). In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 3 months, 12 months, 18 months and preferably 24 months when stored at 25 degrees Celsius (25C) and 60 % relative humidity. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 3 months, 18 months and preferably 24 months when stored at 30 degrees Celsius (30C).

[41] The low-dose formulations of the invention comprise an amount of at least one GCC agonist peptide per unit dose that is less than 10 mg. It is especially advantageous to formulate oral compositions in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage form" as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved. In one embodiment, the unit dosage form is a tablet or a capsule.

[42] In one embodiment of the low-dose formulations of the invention, the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg, 9.5 mg, or 10 mg.

[43] In one embodiment, the low-dose formulation contains a carrier that is non-hygroscopic. In one embodiment, the carrier is selected from mannitol and maltose (e.g., ADVANTOSE 100).

[44] In one embodiment, the carrier is cellulose, preferably microcrystalline cellulose (e.g., Avicel PH 102, low moisture Avicel PH 112, Avicel PH 200, or Celphere SCP-100). In one embodiment, the carrier is calcium phosphate or calcium sulphate. In another embodiment, the carrier is a saccharide. The term "saccharide" as used herein also refers to polysaccharides. Thus, the term saccharide is meant to include polysaccharides. In one embodiment, the saccharide is selected from mannitol, trehalose, lactose, sucrose, sorbitol, and maltose. In a preferred embodiment, the saccharide is mannitol. Preferably the saccharide has a low water content, a small particle size and a narrow particle-size distribution.

[45] Carriers having small particle sizes, and/or spherical shape, and narrow size distribution are preferred. Particles of less than 20 microns have a relatively high surface area to volume ratio causing inter-particle attractive forces to dominate and resist bulk flow. Larger particles (greater than 100 microns) tend to roll or slide over one another and exhibit superior bulk flow properties compared with small particles. A narrow particle-size distribution reduces particle packing and increases flow. In one embodiment, the particles are between 20 and 500 microns in size (as measured across the largest diameter of the particle, on average). In one embodiment, a small particle size and a narrow particle size range refers to particles having a size range of from 20-300 microns, 50-200 microns, or 75-150 microns. In certain embodiments, the carrier has a substantially spherical shape such as can be obtained with a spray drying process.

[46] In one embodiment, the low-dose formulation is a solid formulation and the unit dose is in the form of a tablet or capsule. In one embodiment, the low-dose formulation is a liquid formulation and the unit dosage form is a liquid-filled capsule. In one embodiment, the

liquid formulation in the form of a solution or suspension of the GCC agonist peptide in an lipophilic liquid. Examples of suitable liquids include medium chain triglycerides (e.g., LABRAFAC Lipophile), propylene glycol dicaprylocaprate (e.g., LABRAFAC PG), vitamin E (e.g., α tocopherol), PEG 400 (e.g., Polyethylene glycol low M.W. (liquid)), propylene glycol, soybean oil, and Castor oil. In one embodiment, the liquid is selected from the group consisting of medium chain triglycerides, propylene glycol dicaprylocaprate, vitamin E, and soybean oil. In one embodiment, the refined specialty oil is selected from Arachis oil, Castor oil, cottonseed oil, maize (corn) oil, olive oil, sesame oil, soybean oil, and sunflower oil. In one embodiment, the medium chain triglyceride or related ester is AKOMED E, AKOMED R, CAPTEX 355, LABRAFAC CC, LABRAFAC PG, LAUROGLYCOL FCC, MIGLYOL 810, MIGLYOL 812, MIGLYOL 829, MIGLYOL 840, and SOFTISAN 645.

[47] A formulation according to the invention may be contained in a blister pack. In a particular embodiment, the powder, tablet, or capsule comprising the formulation is contained in a blister pack. Preferably, the blister pack is made of a material that allows only minimal permeation by water vapor and oxygen. In one embodiment the blister pack is comprised of a metal foil. In one embodiment, the blister pack is comprised of ACLAR. In one embodiment, the container of the blister pack is flushed with an inert gas such as nitrogen or argon. In one embodiment, the container further includes a desiccant. In one embodiment, the desiccant is calcium chloride. In one embodiment the desiccant is a molecular sieve.

[48] While any GCC agonist known in the art can be formulated according to the present invention, analogs of uroguanylin and bacterial ST peptides are preferred. In certain embodiments, the uroguanylin and bacterial ST peptide analogs have superior properties compared to naturally occurring, or "wild-type" peptides. For example, the uroguanylin and bacterial ST peptides for use in the present invention are preferably modified to increase their resistance to degradation at the N-terminus and C-terminus from carboxypeptidases, aminopeptidases, and/or by other proteolytic enzymes present in the stimulated human intestinal juices and human gastric juices. In certain embodiments, the GCC agonist formulation comprises a peptide consisting essentially of an amino acid sequence selected from SEQ ID NOs: 1-249. In a preferred embodiment, the peptide consists essentially of an amino acid sequence selected from SEQ ID NOs: 1, 8, 9, 55 and 56. The term "consists essentially of" refers to a peptide that is identical to the reference peptide in its amino acid

sequence or to a peptide that does not differ substantially in terms of either structure or function from the reference peptide. A peptide differs substantially from the reference peptide if its primary amino acid sequence varies by more than three amino acids from the reference peptide or if its activation of cellular cGMP production is reduced by more than 50% compared to the reference peptide. Preferably, substantially similar peptides differ by no more than two amino acids and not by more than about 25% with respect to activating cGMP production. In preferred embodiments, the GCC agonist is a peptide comprising at least 12 amino acid residues, and most preferably comprising between 12 and 26 amino acids. Non-limiting examples of such analogs of uroguanylin and bacterial ST peptides are described in Section 1.2 below.

[49] The invention provides methods for treating or preventing certain diseases and disorders and methods for increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. The term "treating" as used herein refers to a reduction, a partial improvement, amelioration, or a mitigation of at least one clinical symptom associated with the gastrointestinal disorders being treated. The term “preventing” refers to an inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorders to be prevented. The term "effective amount” as used herein refers to an amount that provides some improvement or benefit to the subject. In certain embodiments, an effective amount is an amount that provides some alleviation, mitigation, and/or decrease in at least one clinical symptom of the gastrointestinal disorder to be treated. In other embodiments, the effective amount is the amount that provides some inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorder to be prevented. The therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. The term “subject” preferably refers to a human subject but may also refer to a non-human primate or other mammal preferably selected from among a mouse, a rat, a dog, a cat, a cow, a horse, or a pig.

[50] In accordance with the methods of the present invention, the GCC agonist formulation can be administered alone or in combination with one or more additional therapeutic agents to prevent or treat inflammation, cancer and other disorders, particularly of the gastrointestinal tract. In a preferred embodiment, the GCC agonist formulation is administered for the treatment of chronic constipation. In one embodiment, the GCC agonist

formulation is administered in combination with one or more additional therapeutic agents selected from the group consisting of phosphodiesterase inhibitors, cyclic nucleotides (such as cGMP and cAMP), a laxative (such as SENNA, METAMUCIL, MIRALAX, PEG, or calcium polycarbophil), a stool softener, an anti-tumor necrosis factor alpha therapy for IBD (such as REMICADE, ENBREL, or HUMAIRA), and anti-inflammatory drugs (such as COX-2 inhibitors, sulfasalazine, 5-ASA derivatives and NSAIDS). In certain embodiments, the GCC agonist formulation is administered in combination with an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said GCC agonist. cGMP-PDE inhibitors include, for example, suldinac sulfone, zaprinast, motapizone, vardenifil, and sildenafil. In another embodiment, the GCC agonist formulation is administered in combination with inhibitors of cyclic nucleotide transporters.

1.1 Formulations

[51] The formulations of the invention contain one or more GCC agonist peptides described herein, in combination with one or more pharmaceutically acceptable carriers (also referred to as diluents) and/or excipients. In a preferred embodiment, the formulations of the invention include an inert carrier. The inert carrier is preferably non-hygroscopic. In one embodiment, the carrier in the formulation contains few or no reducing sugars and is substantially free of contaminants including, but not limited to, iron, peroxide, and formaldehyde. In one embodiment, the carrier is selected from the group consisting of sorbitol, mannitol, EMDEX, and starch. In one embodiment, the carrier is mannitol (e.g., MANNOGEM) or microcrystalline cellulose (e.g. PROSOLV, CELPHERE, CELPHERE beads).

[52] The low-dose formulations of the invention contain no greater than 10 mg per unit dose of a GCC agonist peptide. The remainder of the formulation is comprised of the carrier and one or more optional excipients. In one embodiment, the amount of carrier is at least 90% of the total weight of the formulation. In another embodiment, the amount of carrier is at least 95% or at least 98% of the total weight of the formulation. In one embodiment, the amount of carrier is between 90 and 99.9% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise a disintegrant which is present at

1 to 5% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise a lubricant which is present at 0.02 to 5% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise an amino acid such as arginine, leucine, isoleucine, valine, histidine, phenylalanine, alanine, glutamic acid, aspartic acid, glutamine, methionine, asparagine, tyrosine, threonine, tryptophan, or glycine, which is present at 0.1 to 4% (e.g., 0.1-1%) of the total weight of the formulation. In one embodiment, the molar ratio between the amino acid and the GCC agonist peptide is from about 2:1 to about 30:1 or about 2:1 to about 20:1 (e.g., 5:1). In one embodiment, the one or more optional excipients comprise a stabilizer such as a divalent cation salt, more specifically, a water-soluble divalent cation salt (e.g., calcium chloride, magnesium chloride, zinc chloride, manganese chloride, or calcium ascorbate), which is present at 0.1 to 12% (e.g., 0.1-4%) of the total weight of the formulation. In one embodiment, the molar ratio between the salt and the GCC agonist peptide is from about 5:1 to about 20:1 (e.g., 10:1).

[53] The formulations may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffnose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and polypeptides and proteins, for example albumen.

[54] Further examples of pharmaceutically acceptable carriers and excipients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, antioxidant, and coating agents such as: BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, xanthan, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone (e.g., povidone, crospovidone, copovidone, etc), methyl cellulose, Methocel, pre-gelatinized starch (e.g., STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (FMC Corporation, Marcus Hook, PA, USA), Emdex, Plasdone, or mixtures thereof, FILLERS: talc, calcium carbonate (e.g., granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, dextrose, fructose, honey, lactose anhydrate, lactose monohydrate, lactose and

aspartame, lactose and cellulose, lactose and microcrystalline cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose & guar gum, molasses, sucrose,or mixtures thereof, DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate (such as Explotab), potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums (like gellan), low-substituted hydroxypropyl cellulose, ploy plasdone, or mixtures thereof, LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, compritol, stearic acid, sodium lauryl sulfate, sodium stearyl fumarate (such as Pruv), vegetable based fatty acids lubricant, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Piano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof, ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof, ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, ANTOXIDANTS: ascorbic acid, BHA, BHT, EDTA, or mixture thereof, and COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, gellan gum, maltodextrin, methacrylates, microcrystalline cellulose and carrageenan or mixtures thereof.

[55] The formulation can also include other excipients and categories thereof including but not limited to Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, protease inhibitors (e.g. soybean trypsin inhibitor, organic acids), pH lowering agents, creams and lotions (like maltodextrin and carrageenans); materials for chewable

tablets (like dextrose, fructose, lactose monohydrate, lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spheronization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD&C Yellow No. 6 aluminum lake, FD&C Blue # 1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6 Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol, methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

[56] Solid oral dosage forms may optionally be treated with coating systems (e.g. Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS- 1-7040), and black ink (S- 1-8 106).

[57] The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Other sustained release formulations and polymers for use in the compositions and methods of the invention are described in EP 0 467 389 A2, WO 93/24150, U.S.

5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 97/26015, WO 97/04744, and US20020019446. In such sustained release formulations microparticles (Delie and Blanco-Prieto 2005 Molecule 10:65-80) of polypeptide are combined with microparticles of polymer. U.S. 6,011,0 1 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (i.e. PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled releaseof the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224 materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon including those described in US4,910,021 and WO9001329. US4910021 describes using a pH-sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175,003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane- coated pellet comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher.

[58] The GCC peptides described herein may be formulated in the pH triggered targeted control release systems described in WO04052339. The agents described herein may be formulated according to the methodology described in any of WO03105812 (extruded hyrdratable polymers); WO0243767 (enzyme cleavable membrane translocators); WO03007913 and WO03086297 (mucoadhesive systems); WO02072075 (bilayer laminated

formulation comprising pH lowering agent and absorption enhancer); WO04064769 (amidated polypeptides); WO05063156 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms); US5007790 and US5972389 (sustained release dosage forms); WO041 1271 1 (oral extended release compositions); WO05027878, WO02072033, and WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952,314 (biopolymer); US5,108,758 (glassy amylose matrix delivery); US 5,840,860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material such as wheat gliadin or zein); US 5,866,619 and US 6,368,629 (saccharide containing polymer); US 6,531,152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (e.g. hydrophobic polymer-Eudragrit)); US 6,234,464; US 6,403,130 (coating with polymer containing casein and high methoxy pectin; WO0174 175 (Maillard reaction product); WO05063206 (solubility increasing formulation); WO040 19872 (transferring fusion proteins).

[59] The GCC peptides described herein may be formulated using gastrointestinal retention system technology (GIRES; Merrion Pharmaceuticals). GIRES comprises a controlled-release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. The capsule shell can be a HPMC capsule shell or Gelatin capsule shell. Upon dissolution of the capsule, a gas-generating system inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing agents described herein.

[60] The GCC peptides described herein can also be formulated using the multi matrix system technology (MMX).

[61] The GCC peptides described herein can be formulated in an osmotic device including the ones disclosed in US 4,503,030, US 5,609,590 and US 5,358,502. US 4,503,030 discloses an osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract. More particularly, the invention relates to an osmotic device comprising a wall formed of a semi-permeable pH sensitive composition that surrounds a compartment containing a drug, with a passageway through the wall connecting the exterior of the device with the compartment. The device delivers the drug at a controlled rate in the region of the

gastrointestinal tract having a pH of less than 3.5, and the device self- destructs and releases all its drug in the region of the gastrointestinal tract having a pH greater than 3.5, thereby providing total availability for drug absorption. U.S. Patent Nos. 5,609,590 and 5, 358,502 disclose an osmotic bursting device for dispensing a beneficial agent to an aqueous environment. The device comprises a beneficial agent and osmagent surrounded at least in part by a semi-permeable membrane. The beneficial agent may also function as the osmagent. The semi-permeable membrane is permeable to water and substantially impermeable to the beneficial agent and osmagent. A trigger means is attached to the semi-permeable membrane (e.g., joins two capsule halves). The trigger means is activated by a pH of from 3 to 9 and triggers the eventual, but sudden, delivery of the beneficial agent. These devices enable the pH-triggered release of the beneficial agent core as a bolus by osmotic bursting.

[62] In one embodiment the formulation contains a GCC agonist peptide, mannitol, silicified microcrystalline cellulose, sodicum starch glycolate, and sodium stearyl fumarate. The GCC agonist is at a concentration of less than 5% w/w, less than 4%, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.23% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The mannitol is at a concentration of at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, or at least 80% w/w. In some embodiments the mannitol is present at about 79% w/w (e.g., 79.77%). The mannitol is preferably Mannogem EZ. The silicified microcrystalline cellulose is at a concentration of at least 5% w/w, at least 10% w/w, or at least 15% w/w. In some embodiments the concentration of the silicified microcrystalline cellulose is about 15% w/w. The silicified microcrystalline cellulose is preferably Prosolv SMCC 90 LM. The sodicum starch glycolate is at a concentration of at least 1% w/w, at least 2% w/w, at least 3% w/w, or at least 4% w/w. In some embodiments the concentration of the sodicum starch glycolate is about 4% w/w. The sodicum starch glycolate is preferably Explotab. The sodium stearyl fumarate is at a concentration of at least 0.2% w/w, at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9, or at least 1% w/w. In some embodiments the concentration of the sodium stearyl fumarate is about 1% w/w. The sodium stearyl fumarate is preferably Pruv.

[63] In one embodiment the formulation contains a GCC agonist peptide, silicified microcrystalline cellulose, and sodicum starch glycolate. The GCC agonist is at a

concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.3% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The silicified microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, or at least 95% w/w. In some embodiments the concentration of the silicified microcrystalline cellulose is about 95.7% w/w. The silicified microcrystalline cellulose is preferably Prosolv SMCC 90 HD. The sodicum starch glycolate is at a concentration of at least 1% w/w, at least 2% w/w, at least 3% w/w, or at least 4% w/w. In some embodiments the concentration of the sodicum starch glycolate is 4% w/w. The sodicum starch glycolate is preferably Explotab.

[64] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, calcium chloride dihydrate, leucine, and hyrpomellose. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.3246% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 99.10% w/w. The microcrystalline cellulose is preferably Celphere SCP-100. The calcium chloride dihydrate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the calcium chloride dihydrate is about 0.2622% w/w. The leucine is at a concentration of at least 0.05% w/w, at least 0.1% w/w, at least 0.12% w/w, or at least 0.15% w/w. In some embodiments the concentration of leucine is about 0.12% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the hypromellose is about 0.2% w/w. The hypromellose is preferably Methocel E5 PremLV.

[65] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, calcium chloride dihydrate, leucine, hypromellose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some

embodiments the GCC peptide is at a concentration of about 0.36% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.75% w/w. The microcrystalline cellulose is preferably Avicel PH 102. The calcium chloride dihydrate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, at least 0.25% w/w, or at least 0.3% w/w. In some embodiments the concentration of the calcium chloride dihydrate is about 0.29% w/w. The leucine is at a concentration of at least 0.05% w/w, at least 0.1% w/w, at least 0.12% w/w, or at least 0.15% w/w. In some embodiments the concentration of leucine is about 0.13% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the hypromellose is about 0.22% w/w. The hypromellose is preferably Methocel E5 PremLV. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[66] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.32% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 99.43% w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[67] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a

concentration of about 0.32% w/w, about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.57 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[68] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 97.09 % w/w. The microcrystalline cellulose is preferably Avicel PH 112. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[69] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, histidine, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.48% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is

0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5% w/w. The hypromellose is preferably Methocel ES Premium LV. The histine is a concentration of at least 0.6% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, at least 3% w/w, or at least 5% w/w. In some embodiments the concentration of the histidine is 1-6% w/w. In a particular embodiment, the concentration of the arginine is 1.48% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.09% w/w, or at least 0.1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[70] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, arginine, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.17% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.31% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is

0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5% w/w. The hypromellose is preferably Methocel ES Premium LV. The arginine is a concentration of at least 0.5% w/w, at least 1% w/w, at least 1.5% w/w, or at least 2% w/w. In some embodiments the concentration of the arginine is 1-6% w/w. In a particular embodiment, the concentration of the arginine is 1.66% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.09% w/w, or at least 0.1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[71] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, TRIS, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.17% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.81% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is 0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5%

w/w. The hypromellose is preferably Methocel ES Premium LV. The TRIS is a concentration of at least 0.6% w/w, at least 0.8% w/w, at least 0.9% w/w, or at least 1% w/w. In some embodiments the concentration of the TRIS is 0.5-6% w/w. In a particular embodiment, the concentration of the arginine is 1.15% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.1% w/w, or at least 1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[72] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.10% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.64 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[73] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5%

w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 3.32% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 96.43 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

1.2 GCC Agonists

[74] The GCC agonists for use in the formulations and methods of the invention bind to guanylate cyclase C and stimulate intracellular production of cGMP. Optionally, the GCC agonists induce apoptosis and inhibit proliferation of epithelial cells. The term, "guanylate cyclase C" refers to a transmembrane form of guanylate cyclase that acts as the intestinal receptor for the heat-stable toxin (ST) peptides secreted by enteric bacteria. Guanylate cyclase C is also the receptor for the naturally occurring peptides guanylin and uroguanylin. The possibility that there may be different receptors for each of these peptides has not been excluded. Hence, the term "guanylate cyclase C" may also encompass a class of transmembrane guanylate cyclase receptors expressed on epithelial cells lining the gastrointestinal mucosa.

[75] The term "GCC agonist" refers to both peptides and non-peptide compounds such as that bind to an intestinal guanylate cyclase C and stimulate the intracellular production of cGMP. Where the GCC agonist is a peptide, the term encompasses biologically active fragments of such peptides and pro-peptides that bind to guanylate cyclase C and stimulate the intracellular production of cGMP.

[76] Preferably, the GCC agonists for use in the formulations and methods of the invention stimulate intracellular cGMP production at higher levels than naturally occurring GCC agonists such as uroguanylin, guanylin, and ST peptides. In some embodiments, the GCC agonists stimulate intracellular cGMP production at higher levels than the peptide designated

SP-304 (SEQ ID NO:1). In specific embodiments, a GCC agonist for use in the formulations and methods of the invention stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to uroguanylin, guanylin, lymphoguanylin, linaclotide, ST peptides, or SP-304. The terms "induce" and "stimulate"are used interchangeably throughout the specification.

[77] Preferably, the GCC agonists for use in the formulations and methods of the invention are more stable than naturally occurring GCC agonists such as uroguanylin, guanylin, and ST peptides. In some embodiments, the GCC agonists are more stable than the peptide designated SP-304. "Stability" in this context refers to resistance to degradation in gastrointestinal fluid and/or intestinal fluid (or simulated gastrointestinal or intestinal fluids) compared to the reference peptide. For example, the GCC agonists for use in the formulations and methods of the invention preferably degrade 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GCC angonists and/or SP-304.

[78] The GCC agonists for use in the formulations and methods of the invention are preferably peptides. In some embodiments, the GCC agonist peptide is less than 30 amino acids in length. In particular embodiments, the GCC agonist peptide is less than or equal to 30, 25, 20, 15, 14, 13, 12, 11, 10, or 5 amino acids in length. Examples of GCC agonist peptides for use in the formulations and methods of the invention include those described in U.S. Serial Nos.: 12/133,344, filed June 4, 2008, 12/478505, filed June 4, 2009; 12/478511, filed June 4, 2009; 12/504288, filed July 16, 2009; and U.S. Provisional Application Serial Nos.: 60/933194, filed June 4, 2007; 61/058,888, filed June 4, 2008; 61/058,892, filed June 4, 2008; and 61/081,289, filed July 16, 2008, each of which is incorporated by reference herein in its entirety.

[79] Specific examples of GCC agonist peptides for use in the formulations and methods of the invention include those described in Tables I-VII below. As used Tables I-VII, the terms "PEG3" or "3PEG" refer to a polyethylene glycol such as aminoethyloxy-ethyloxy-acetic acid (AeeA), and polymers thereof. The term "X_{aa}" refers to any natural or unnatural amino acid or amino acid analogue. The term "M_{aa}" refers to a cysteine (Cys), penicillamine (Pen) homocysteine, or 3-mercaptoproline. The term "Xaa_{n1}" is meant to denote an amino acid sequence of any natural or unnatural amino acid or amino acid analogue that is one, two

or three residues in length; Xaa_{n2} is meant to denote an amino acid sequence that is zero or one residue in length; and Xaa_{n3} is meant to denote an amino acid sequence zero, one, two, three, four , five or six residues in length. Additionally, any amino acid represented by Xaa, Xaa_{n1}, $Xaa_{n2,\ or}$ Xaa_{n3} may be an L-amino acid, a D-amino acid, a methylated amino acid or any combination of thereof. Optionally, any GCC agonist peptide represented by Formulas I to XX in the tables may contain on or more polyethylene glycol residues at the the N-terminus, C-terminus or both.

[80] In certain embodiments, a GCC agonist formulation of the invention comprises a peptide selected from SEQ ID NOs: 1-249, the sequences of which are set forth below in Tables I to VII below. In one embodiment, a GCC agonist formulation comprises the peptide designated by SEQ ID NOs:1, 8, 9, 55, or 56.

[81] In certain embodiments, a GCC agonist formulation of the invention comprises a peptide that is substantially equivalent to a peptide selected from SEQ ID NOs: 1-249. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to an intestinal guanylate cyclase receptor and stimulate fluid and electrolyte transport.

1.2.1 GCC Agonist Peptides

[82] In a preferred embodiment, the GCC agonists for use in the formulations and methods of the invention are GCC agonist peptides. In certain embodiments, the GCC agonist peptides are analogues of uroguanylin or a bacterial ST peptide. Uroguanylin is a circulating peptide hormone with natriuretic activity. An ST peptide is a member of a family of heat stable enterotoxins (ST peptides) secreted by pathogenic strains of *E. coli* and other enteric bacteria that activate guanylate cyclase receptor and cause secretory diarrhea. Unlike bacterial ST peptides, the binding of uroguanylin to guanylate cyclase receptor is dependent on the physiological pH of the gut. Therefore, uroguanylin is expected to regulate fluid and electrolyte transport in a pH dependent manner and without causing severe diarrhea.

[83] The GCC agonist peptides for use in the formulations and methods of the invention can be polymers of L-amino acids, D-amino acids, or a combination of both. For example, in various embodiments, the peptides are D retro-inverso peptides. The term "retro-inverso

isomer" refers to an isomer of a linear peptide in which the direction of the sequence is reversed and the chirality of each amino acid residue is inverted. *See, e.g.*, Jameson *et al.*, *Nature*, 368, 744-746 (1994); Brady *et al.*, Nature, 368, 692-693 (1994). The net result of combining D-enantiomers and reverse synthesis is that the positions of carbonyl and amino groups in each amide bond are exchanged, while the position of the side-chain groups at each alpha carbon is preserved. Unless specifically stated otherwise, it is presumed that any given L-amino acid sequence of the invention may be made into a D retro-inverso peptide by synthesizing a reverse of the sequence for the corresponding native L-amino acid sequence.

[84] The GCC agonist peptides for use in the formulations and methods of the invention are able to induce intracellular cGMP production in cells and tissues expressing guanylate cyclase C. In certain embodiments, the GCC agonist peptide stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to naturally occurring GCC agonists such as uroguanylin, guanylin, or ST peptides. Optionally, the GCC agonist peptide stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared SP-304 (SEQ ID NO:1). In further embodiments, the GCC agonist peptide stimulates apoptosis, *e.g.*, programmed cell death, or activate the cystic fibrosis transmembrane conductance regulator (CFTR).

[85] In some embodiments, the GCC agonist peptides for use in the formulations and methods of the invention are more stable than naturally occurring GCC agonists and/or SP-304 (SEQ ID NO:1), SP-339 (linaclotide) (SEQ ID NO: 55) or SP-340 (SEQ ID NO: 56). For example, the GCC agonist peptide degrades 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GCC agonists and/or SP-304, SP-339 (linaclotide) or SP-340. In certain embodiments, the GCC agonist peptides for use in the formulations and methods of the invention are more stable to proteolytic digestion than naturally occurring GCC agonists and/or SP-304 (SEQ ID NO:1), SP-339 (linaclotide) (SEQ ID NO: 55) or SP-340 (SEQ ID NO: 56). In one embodiment, a GCC agonist peptide is pegylated in order to render the peptides more resistant towards protealysis by enzymes of the gastrointestinal tract. In a preferred embodiment, the GCC agonist peptide is pegylated with the aminoethyloxy-ethyloxy-acetic acid (Aeea) group at its C-terminal end, at its N-terminal end, or at both termini.

[86] Specific examples of GCC agonist peptides that can be used in the methods and formulations of the invention include a peptide selected from the group designated by SEQ ID NOs: 1-249.

[87] In one embodiment, the GCC agonist peptide is a peptide having the amino acid sequence of any one of Formulas X- XVII (*e.g.* SEQ ID NO:87-98).

[88] In some embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula I, wherein at least one amino acid of Formula I is a D-amino acid or a methylated amino acid and/or the amino acid at position 16 is a serine. Preferably, the amino acid at position 16 of Formula I is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 of Formula I is a d-leucine or a d-serine. Optionally, one or more of the amino acids at positions 1-3 of Formula I are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn^1, Asp^2 or Glu^3 (or a combination thereof) of Formula I is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula I is a leucine, serine or tyrosine.

[89] In alternative embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula II, wherein at least one amino acid of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted by Xaa_{n2} of Formula II is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula II is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula II is a leucine, a serine, or a tyrosine.

[90] In some embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula III, wherein at least one amino acid of Formula III is a D-amino acid or a methylated amino acid and/or Maa is not a cysteine. Preferably, the amino acid denoted by Xaa_{n2} of Formula III is a D-amino acid or a methylated amino acid. In some embodiments the amino acid denoted by Xaa_{n2} of Formula III is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula III is a D-

amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula III is a leucine, a serine, or a tyrosine.

[91] In other embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula IV, wherein at least one amino acid of Formula IV is a D-amino acid or a methylated amino acid, and/or Maa is not a cysteine. Preferably, the Xaa_{n2} of Formula IV is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula IV is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more of the amino acids denoted by Xaa_{n1} of Formula IV is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted Xaa^6 of Formula IV is a leucine, a serine, or a tyrosine.

[92] In further embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula V, wherein at at least one amino acid of Formula V is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 (i.e., Xaa^{16}) of Formula V is a d-leucine or a d-serine. Optionally, one or more of the amino acids at position 1-3 of Formula V are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn^1, Asp^2 or Glu^3 (or a combination thereof) of Formula V is a D-amino acids or a methylated amino acid. Preferably, the amino acid denoted at Xaa^6 of Formula V is a leucine, a serine, or a tyrosine.

[93] In additional embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula VI, VII, VIII, or IX. Preferably, the amino acid at position 6 of Formula VI, VII, VIII, or IX is a leucine, a serine, or a tyrosine. In some aspects the amino acid at position 16 of Formula VI, VII, VIII, or IX is a leucine or a serine. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid.

[94] In additional embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula X, XI, XII, XIII, XIV, XV, XVI or XVII. Optionally, one or more amino acids of Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a methylated amino acid. Preferably, the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a

methylated amino acid. For example the the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-tyrosine.

[95] Preferably, the amino acid denoted by Xaa^6 of Formula XIV is a tyrosine, phenyalanine or a serine. Most preferably the amino acid denoted by Xaa^6 of Formula XIV is a phenyalanine or a serine. Preferably, the amino acid denoted by Xaa^4 of Formula XV, XVI or XVII is a tyrosine, a phenyalanine, or a serine. Most preferably, the amino acid position Xaa^4 of Formula V, XVI or XVII is a phenyalanine or a serine.

[96] In some embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XVIII. Preferably, the amino acid at position 1 of Formula XVIII is a glutamic acid, aspartic acid, glutamine or lysine. Preferably, the amino acid at position 2 and 3 of Formula XVIII is a glutamic acid, or an aspartic acid. Preferably, the amino acid at position 5 a glutamic acid. Preferably, the amino acid at position 6 of Formula XVIII is an isoleucine, valine, serine, threonine or tyrosine. Preferably, the amino acid at position 8 of Formula XVIII is a valine or isoleucine. Preferably, the amino acid at position 9 of Formula XVIII is a an asparagine. Preferably, the amino acid at position 10 of Formula XVIII is a valine or an methionine. Preferably, the amino acid at position 11 of Formula XVIII is an alanine. Preferably, the amino acid at position 13 of Formula XVIII is a threonine. Preferably, the amino acid at position 14 of Formula XVIII is a glycine. Preferably, the amino acid at position 16 of Formula XVIII is a leucine, serine or threonine

[97] In alternative embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XIX. Preferably, the amino acid at position 1 of Formula XIX is a serine or asparagine. Preferably, the amino acid at position 2 of Formula XIX is a histidine or an aspartic acid. Preferably, the amino acid at position 3 of Formula XIX is a threonine or a glutamic acid. Preferably, the amino acid at position 5 of Formula XIX is a glutamic acid. Preferably, the amino acid at position 6 of Formula XIX is an isoleucine, leucine, valine or tyrosine. Preferably, the amino acid at position 8, 10, 11, or 13 of Formula XIX is a alanine. Preferably, the amino acid at position 9 of Formula XIX is an asparagine or a phenylalanine. Preferably, the amino acid at position 14 of Formula XIX is a glycine.

[98] In further embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XX. Preferably, the amino acid at position 1 of Formula XX is a

glutamine. Preferably, the amino acid at position 2 or 3 of Formula XX is a glutamic acid or a aspartic acid. Preferably, the amino acid at position 5 of Formula XX is a glutamic acid. Preferably, the amino acid at position 6 of Formula XX is threonine, glutamine, tyrosine, isoleucine, or leucine. Preferably, the amino acid at position 8 of Formula XX is isoleucine or valine. Preferably, the amino acid at position 9 of Formula XX is asparagine. Preferably, the amino acid at position 10 of Formula XX is methionine or valine. Preferably, the amino acid at position 11 of Formula XX is alanine. Preferably, the amino acid at position 13 of Formula XX is a threonione. Preferably, the amino acid at position 1 of Formula XX is a glycine. Preferably, the amino acid at position 15 of Formula XX is a tyrosine. Optionally, the amino acid at position 15 of Formula XX is two amino acid in length and is Cysteine (Cys), Penicillamine (Pen) homocysteine, or 3-mercaptoproline and serine, leucine or threonine.

[99] In certain embodiments, one or more amino acids of the GCC agonist peptides are replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. Such amino acids and amino acid analogs are known in the art. See, for example, Hunt, "The Non-Protein Amino Acids," in *Chemistry and Biochemistry of the Amino Acids*, Barrett, Chapman and Hall, 1985. In some embodiments, an amino acid is replaced by a naturally-occurring, non-essential amino acid, *e.g.*, taurine. Non-limiting examples of naturally occurring amino acids that can be replaced by non-protein amino acids include the following: (1) an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr); (2) Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, *e.g.*, a halogen, -CH3, -OH, -CH2NH3, -C(O)H, -CH2CH3, - CN, -CH2CH2CH3, -SH, or another group; (3) glutamine residues can be substituted with gamma-Hydroxy-Glu or gamma- Carboxy-Glu; (4) tyrosine residues can be substituted with an alpha substituted amino acid such as L-alpha-methylphenylalanine or by analogues such as: 3-Amino-Tyr; Tyr(CH3); Tyr(PO3(CH3)2); Tyr(SO3H); beta-Cyclohexyl-Ala; beta-(l-Cyclopentenyl)-Ala; beta- Cyclopentyl-Ala; beta-Cyclopropyl-Ala; beta-Quinolyl-Ala; beta-(2-Thiazolyl)-Ala; beta- (Triazole-l-yl)-Ala; beta-(2-Pyridyl)-Ala; beta-(3-Pyridyl)-Ala; Amino-Phe; Fluoro-Phe; Cyclohexyl-Gly; tBu-Gly; beta-(3-benzothienyl)-Ala; beta-(2-thienyl)-Ala; 5-Methyl-Trp; and A- Methyl-Trp; (5) proline residues can be substituted with homopro (L-pipecolic acid); hydroxy-Pro; 3,4-Dehydro-Pro; 4-fluoro-Pro; or alpha-methyl-

Pro or an N(alpha)-C(alpha) cyclized amino acid analogues with the structure: n = 0, 1, 2, 3; and (6) alanine residues can be substituted with alpha-substitued or N-methylated amino acid such as alpha-amino isobutyric acid (aib), L/D-alpha-ethylalanine (L/D-isovaline), L/D-methylvaline, or L/D-alpha-methylleucine or a non-natural amino acid such as beta-fluoro-Ala. Alanine can also be substituted with: n = 0, 1, 2, 3 Glycine residues can be substituted with alpha-amino isobutyric acid (aib) or L/D-alpha- ethylalanine (L/D-isovaline).

[100] Further examples of non-natural amino acids include: an unnatural analog of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid, or any combination thereof; an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; an amino acid that is amidated at a site that is not naturally amidated, a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (*e.g.*, an amino acid containing deuterium, tritium, ^{13}C, ^{15}N, or ^{18}O); a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, *e.g.*, a sugar substituted serine or the like; a carbon-linked sugar-containing amino acid; a redox-**active amino acid; an α-hydroxy containing acid; an amino thio acid containing amino acid; an α, α disubstituted amino acid; a β- amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2- naphthyl)alanine; a 3-methyl-phenylalanine; a ρ-acetyl-L-phenylalanine; an O-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAc β -** serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a p-azido-L-phenylalanine; a p-acyl-L-phenylalanine; a p- benzoyl-L-phenylalanine; an L-phosphoserine; a phosphonoserine; a phosphonotyrosine; a p- iodo-phenylalanine; a 4-fluorophenylglycine; a p-bromophenylalanine; a p-amino-L- phenylalanine; an isopropyl-L-phenylalanine; L-3-(2-naphthyl)alanine; D- 3-(2-naphthyl)alanine (dNal); an amino-, isopropyl-, or O-allyl-

containing phenylalanine analogue; a dopa, 0-methyl-L-tyrosine; a glycosylated amino acid; a p-(propargyloxy)phenylalanine; dimethyl-Lysine; hydroxy-proline; mercaptopropionic **acid; methyl-lysine; 3-nitro-tyrosine; norleucine; pyro-glutamic acid; Z (Carbobenzoxyl); ε-Acetyl-Lysine; β-alanine; aminobenzoyl derivative; aminobutyric acid (Abu); citrulline;** aminohexanoic acid; aminoisobutyric acid (AIB); cyclohexylalanine; d-cyclohexylalanine; hydroxyproline; nitro-arginine; nitro-phenylalanine; nitro-tyrosine; norvaline; octahydroindole carboxylate; ornithine (Orn); penicillamine (PEN); tetrahydroisoquinoline; acetamidomethyl protected amino acids and pegylated amino acids. Further examples of unnatural amino acids and amino acid analogs can be found in U.S. 20030108885, U.S. 20030082575, US20060019347 (paragraphs 410-418) and the references cited therein. The polypeptides of the invention can include further modifications including those described in US20060019347, paragraph 589. Exempary GCC agonist peptides which include a non-naturally occurring amino acid include for example SP-368 and SP-369.

[101] In some embodiments, the GCC agonist peptides are cyclic peptides. GCC agonist cyclic peptides can be prepared by methods known in the art. For example, macrocyclization is often accomplished by forming an amide bond between the peptide N- and C-termini, between a side chain and the N- or C-terminus [*e.g.*, with $K_3Fe(CN)_6$ at pH 8.5] (Samson *et al.*, *Endocrinology,* 137: 5182-5185 (1996)), or between two amino acid side chains, such as cysteine. See, *e.g.,* DeGrado, *Adv Protein Chem, 39*: 51-124 (1988). In various embodiments, the GCC agonist peptides are [4,12; 7,15] bicycles.

[102] In certain embodiments, one or both Cys residues which normally form a disulfide bond in a GCC agonist peptide are replaced with homocysteine, penicillamine, 3-mercaptoproline (Kolodziej *et al.* 1996 *Int. J. Pept. Protein Res.* 48:274), **β, β** dimethylcysteine (Hunt *et al.* 1993 *Int. J. Pept. Protein Res.* 42:249), or diaminopropionic acid (Smith *et al.* 1978 *J. Med. Chem.* 2 1:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

[103] In certain embodiments, one or more disulfide bonds in a GCC agonist peptide are replaced by alternative covalent cross-links, *e.g.*, an amide linkage ($-CH_2CH(O)NHCH_2-$ or $-CH_2NHCH(O)CH_2-$), an ester linkage, a thioester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage ($-CH_2CH_2CH_2CH_2-$), an alkenyl linkage ($-CH_2CH=CHCH_2-$), an ether linkage (-

$CH_2CH_2OCH_2$- or -$CH_2OCH_2CH_2$-), a thioether linkage (-$CH_2CH_2SCH_2$- or - $CH_2SCH_2CH_2$-), an amine linkage (-$CH_2CH_2NHCH_2$- or -$CH_2NHCH_2CH_2$-) or a thioamide linkage (-$CH_2CH(S)HNHCH_2$- or -$CH_2NHCH(S)CH_2$-). For example, Ledu *et al.* (*Proc. Natl. Acad. Sci.* 100:11263-78, 2003) describe methods for preparing lactam and amide cross-links. Exemplary GCC agonist peptides which include a lactam bridge include, for example, SP-370.

[104] In certain embodiments, the GCC agonist peptides have one or more conventional polypeptide bonds replaced by an alternative bond. Such replacements can increase the stability of the polypeptide. For example, replacement of the polypeptide bond between a residue amino terminal to an aromatic residue (*e.g.* Tyr, Phe, Trp) with an alternative bond can reduce cleavage by carboxy peptidases and may increase half-life in the digestive tract. Bonds that can replace polypeptide bonds include: a retro-inverso bond (C(O)-NH instead of NH-C(O); a reduced amide bond (NH-CH_2); a thiomethylene bond (S-CH_2 or CH_2-S); an oxomethylene bond (O-CH_2 or CH_2-O); an ethylene bond (CH_2-CH_2); a thioamide bond (C(S)-NH); a trans-olefine bond (CH=CH); a fiuoro substituted trans-olefme bond (CF=CH); a ketomethylene bond (C(O)-CHR or CHR-C(O) wherein R is H or CH_3; and a fluoro-ketomethylene bond (C(O)-CFR or CFR-C(O) wherein R is H or F or CH_3.

[105] In certain embodiments, the GCC agonist peptides are modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceeding. In one aspect described herein, there may be more than one type of modification on the polypeptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cys3 or Cys5. The GCC agonist peptides described herein may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysine, modification by 7-Amino-4-methyl-coumarin (AMC), flourescein, NBD (7-Nitrobenz-2-Oxa-l,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-l- sulfonic acid), dabcyl, dabsyl, dansyl, texas red, FMOC, and Tamra (Tetramethylrhodamine). The GCC agonist peptides described herein may also be conjugated to, for example, polyethylene glycol (PEG); alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; combinations of PEG, alkyl groups and fatty acid radicals (*See*, U.S. Patent 6,309,633;

Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110); BSA and KLH (Keyhole Limpet Hemocyanin). The addition of PEG and other polymers which can be used to modify polypeptides of the invention is described in US20060 19347 section IX.

[106] A GCC agonist peptide can also be a derivatives of a GCC agonist peptide described herein. For example, a derivative includes hybrid and modified forms of GCC agonist peptides in which certain amino acids have been deleted or replaced. A modification may also include glycosylation. Preferrably, where the modification is an amino acid substitution, it is a conservative substitution at one or more positions that are predicted to be non-essential amino acid residues for the biological activity of the peptide. A "conservative substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

[107] In one embodiment, a GCC agonist peptide described herein is subjected to random mutagenesis in order to identify mutants having biological activity.

[108] In one embodiment, the GCC agonist peptide is substantially homologous is a GCC agonist peptide described herein. Such substantially homologous peptides can be isolated by virtue of cross-reactivity with antibodies to a GCC agonist peptide described herein.

[109] Further examples of GCC agonist peptides that can be used in the methods and formulations of the invention are found in Tables I - VII below.

1.2.2 Preparation of GCC agonist peptides

[110] GCC agonist peptides can be prepared using art recognized techniques such as molecular cloning, peptide synthesis, or site-directed mutagenesis.

[111] Peptide synthesis can be performed using standard solution phase or solid phase peptide synthesis techniques or a combination of both process where segments are synthesized by solid phase and condensed in solution phase, in which a peptide linkage occurs through the direct condensation of the amino group of one amino acid with the carboxy group of the other amino acid with the elimination of a water molecule. Peptide bond synthesis by direct condensation, as formulated above, requires suppression of the reactive character of the amino group of the first and of the carboxyl group of the second amino acid. The masking substituents must permit their ready removal, without inducing breakdown of the labile peptide molecule.

[112] In solution phase synthesis, a wide variety of coupling methods and protecting groups may be used (*See*, Gross and Meienhofer, eds., "The Peptides: Analysis, Synthesis, Biology," Vol. 1-4 (Academic Press, 1979); Bodansky and Bodansky, "The Practice of Peptide Synthesis," 2d ed. (Springer Verlag, 1994)). In addition, intermediate purification and linear scale up are possible. Those of ordinary skill in the art will appreciate that solution synthesis requires consideration of main chain and side chain protecting groups and activation method. In addition, careful segment selection is necessary to minimize racemization during segment condensation. Solubility considerations are also a factor. Solid phase peptide synthesis uses an insoluble polymer for support during organic synthesis. The polymer-supported peptide chain permits the use of simple washing and filtration steps instead of laborious purifications at intermediate steps. Solid-phase peptide synthesis may generally be performed according to the method of Merrifield et al., J. Am. Chem. Soc., 1963, 85:2149, which involves assembling a linear peptide chain on a resin support using protected amino acids. Solid phase peptide synthesis typically utilizes either the Boc or Fmoc strategy, which are well known in the art.

[113] Those of ordinary skill in the art will recognize that, in solid phase synthesis, deprotection and coupling reactions must go to completion and the side-chain blocking groups must be stable throughout the synthesis. In addition, solid phase synthesis is generally most suitable when peptides are to be made on a small scale.

[114] Acetylation of the N-terminal can be accomplished by reacting the final peptide with acetic anhydride before cleavage from the resin. C-amidation is accomplished using an appropriate resin such as methylbenzhydrylamine resin using the Boc technology.

[115] Alternatively the GCC agonist peptides are produced by modern cloning techniques For example, the GCC agonist peptides are produced either in bacteria including, without limitation, E. coli, or in other existing systems for polypeptide or protein production (*e.g.*, Bacillus subtilis, baculovirus expression systems using Drosophila Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized. If the GCC agonist peptide or variant peptide is to be produced in bacteria, *e.g.*, E. coli, the nucleic acid molecule encoding the polypeptide may also encode a leader sequence that permits the secretion of the mature polypeptide from the cell. Thus, the sequence encoding the polypeptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST polypeptide. The secreted, mature polypeptide can be purified from the culture medium.

[116] The sequence encoding a GCC agonist peptide described herein can be inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, E. coli, B subtilis, Pseudomonas, Salmonella. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences.

[117] A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (*e.g.*, an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during polypeptide production.

[118] The protein coding sequence that includes a GCC agonist peptide described herein can also be fused to a nucleic acid encoding a polypeptide affinity tag, *e.g.*, glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag

or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the polypeptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the polypeptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the polypeptide of interest.

[119] Genetic constructs and methods suitable for production of immature and mature forms of the GCC agonist peptides and variants described herein in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce polypeptides in a biological system.

[120] The peptides disclosed herein may be modified by attachment of a second molecule that confers a desired property upon the peptide, such as increased half-life in the body, for example, pegylation. Such modifications also fall within the scope of the term "variant" as used herein.

Table I. GCRA Peptides (SP-304 and Derivatives)

Name	Position of Disulfide bonds	Structure	SEQ ID NO
SP-304	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	1
SP-326	C3:C11, C6:C14	Asp^{1}-Glu^{2}-Cys^{3}-Glu^{4}-Leu^{5}-Cys^{6}-Val^{7}-Asn^{8}-Val^{9}-Ala^{10}-Cys^{11}-Thr^{12}-Gly^{13}-Cys^{14}-Leu^{15}	2
SP-327	C2:C10, C5:C13	Asp^{1}-Glu^{2}-Cys^{3}-Glu^{4}-Leu^{5}-Cys^{6}-Val^{7}-Asn^{8}-Val^{9}-Ala^{10}-Cys^{11}-Thr^{12}-Gly^{13}-Cys^{14}	3
SP-328	C2:C10, C5:C13	Glu^{1}-Cys^{2}-Glu^{3}-Leu^{4}-Cys^{5}-Val^{6}-Asn^{7}-Val^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Leu^{14}	4
SP-329	C2:C10, C5:C13	Glu^{1}-Cys^{2}-Glu^{3}-Leu^{4}-Cys^{5}-Val^{6}-Asn^{7}-Val^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	5
SP-330	C1:C9, C4:C12	Cys^{1}-Glu^{2}-Leu^{3}-Cys^{4}-Val^{5}-Asn^{6}-Val^{7}-Ala^{8}-Cys^{9}-Thr^{10}-Gly^{11}-Cys^{12}-Leu^{13}	6
SP-331	C1:C9, C4:C12	Cys^{1}-Glu^{2}-Leu^{3}-Cys^{4}-Val^{5}-Asn^{6}-Val^{7}-Ala^{8}-Cys^{9}-Thr^{10}-Gly^{11}-Cys^{12}	7
SP332	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	8
SP-333	C4:C12,C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	9
SP-334	C4:C12,C7:C15	dAsn^{1}-dAsp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	10
SP-335	C4:C12,C7:C15	dAsn^{1}-dAsp^{2}-dGlu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	11
SP-336	C4:C12,C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	12
SP-337	C4:C12,C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-dLeu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	13
SP-338	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}	14
SP-342	C4:C12, C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}-PEG3	15
SP-343	C4:C12, C7:C15	PEG3-dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}-PEG3	16
SP-344	C4:C12, C7:C15	PEG3-dAsn^{1}-dAsp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}-PEG3	17
SP-347	C4:C12, C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}-PEG3	18
SP-348	C4:C12, C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	19

SP-350	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	20
SP-352	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	21
SP-358	C4:C12,C7:C15	PEG3-dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	22
SP-359	C4:C12,C7:C15	PEG3-dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	23
SP-360	C4:C12, C7:C15	dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]PEG3	24
SP-361	C4:C12, C7:C15	dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	25
SP-362	C4:C12, C7:C15	PEG3-dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	26
SP-368	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dNal[16]	27
SP-369	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-AIB[8]-Asn[9]-AIB[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	28
SP-370	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Asp[Lactam][7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Orn[15]-dLeu[1]	29
SP-371	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	30
SP-372	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	31
N1	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	32
N2	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	33
N3	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] PEG3	34
N4	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	35
N5	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	36
N6	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	37
N7	C4:C12,C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	38
N8	C4:C12,C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]-PEG3	39
N9	C4:C12,C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	40
N10	C4:C12,C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]-PEG3	41

N11	C4:C12,C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16]-PEG3	42
N12	C4:C12,C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16]	43
N13	C4:C12,C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16]-PEG3	44
Formula I	C4:C12,C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-Xaa[16]	45
Formula II	C4:C12,C7:C15	Xaa_{n1}-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-Xaa_{n2}[16]	46
Formula III	4:12,7:15	Xaa_{n1}-Maa[4]-Glu[5]-Xaa[6]-Maa[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Maa[12]-Thr[13]-Gly[14]-Maa[15] - Xaa_{n2}	47
Formula IV	4:12,7:15	Xaa_{n1} - Maa[4]-Xaa[5]-Xaa[6]- Maa[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]- Maa[12]-Xaa[13]-Xaa[14]- Maa[15]-Xaa_{n2}	48
Formula V	C4:C12,C7:C15	Asn[1]-Asp[2]-Asp[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-Xaa[16]	49
Formula VI	C4:C12,C7:C15	dAsn[1]-Glu[2]-Glu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-X3[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	50
Formula VII	C4:C12,C7:C15	dAsn[1]-dGlu[2]-Asp[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	51
Formula VII	C4:C12,C7:C15	dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	52
Formula VIII	C4:C12,C7:C15	dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Tyr[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	53
Formula IX	C4:C12,C7:C15	dAsn[1]-dGlu[2]-dGlu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Tyr[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	54

Table II. Linaclotide and Derivatives

Name	Position of Disulfide bonds	Structure	SEQ ID NO:
SP-339 (linaclotide)	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	55
SP-340	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	56
SP-349	C1:C6, C2:C10, C5:13	PEG3-Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}-PEG3	57
SP-353	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	58
SP-354	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Phe^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	59
SP-355	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-dTyr^{14}	60
SP-357	C1:C6, C2:C10, C5:13	PEG3-Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	61
SP-374	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	62
SP-375	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	63
SP-376	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	64
SP-377	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	65
SP-378	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	66
SP-379	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	67
SP-380	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	68
SP-381	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Phe^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	69

SP-382	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	70
SP-383	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	71
SP384	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]-PEG3	72
N14	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	73
N15	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]	74
N16	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	75
N17	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	76
N18	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	77
N19	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	78
N20	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	79
N21	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	80
N22	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	81
N23	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	82

N24	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	83
N25	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	84
N26	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu3-Ser[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]	85
N27	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu3-Phe[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]	86
N28	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu3-Ser[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-	87
N29	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu3-Phe[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]	88
N30	1:6, 2:10, 5:13	Pen[1]-Pen[2]-Glu3-Tyr[4]-Pen[5]-Pen[6]-Asn[7]-Pro[8]-Ala[9]-Pen[10]-Thr[11]-Gly[12]-Pen[13]-Tyr[14]	89
N31	1:6, 2:10, 5:13	Pen[1]-Pen[2]-Glu3-Tyr[4]-Pen[5]-Pen[6]-Asn[7]-Pro[8]-Ala[9]-Pen[10]-Thr[11]-Gly[12]-Pen[13]	90
Formula X	C9:C14, C10:C18, C13:21	Xaa[1]-Xaa[2]-Xaa[3]-Xaa[4]-Xaa[5]-Xaa[6]- Asn[7]- Tyr[8]-Cys[9]-Cys[10]-Xaa[11]-Tyr[12]-Cys[13]-Cys[14]-Xaa[15]-Xaa[16]-Xaa[17]-Cys[18]- Xaa[19]-Xaa[20]-Cys[21]-Xaa[22]	91
Formula XI	C9:C14, C10:C18, C13:21	Xaa[1]-Xaa[2]-Xaa[3]-Xaa[4]-Xaa[5]-Xaa[6]-Asn[7]- Phe[8]-Cys[9]-Cys[10] -Xaa[11]-Phe[12]- Cys[13]-Cys[14]-Xaa[15]-Xaa[16]-Xaa[17]-Cys[18]- Xaa[19]-Xaa[20]-Cys[21]-Xaa[22]	92
Formula XII	C3:C8, C4:C12, C7:15	Asn[1]- Phe[2]-Cys[3]-Cys[4] - Xaa[5]-Phe[6]-Cys[7]-Cys[8] - Xaa[9]-Xaa[10]- Xaa[11]-Cys[12]- Xaa[3]-Xaa[14]-Cys[15]-Xaa[16]	93
Formula XIII	3:8, 4:12, C:15	Asn[1]- Phe[2]-Pen[3]-Cys[4] - Xaa[5]-Phe[6]-Cys[7]Pen[8] - Xaa[9]-Xaa[10]- Xaa[11]-Cys12- Xaa[13]-Xaa[14]-Cys[15]-Xaa[16]	94
Formula XIV	3:8, 4:12, 7:15	Asn[1]- Phe[2]-Maa[3]-Maa[4] - Xaa[5]-Xaa[6]-Maa[7]Maa[8] - Xaa[9]-Xaa[10]- Xaa[11]-Maa[12]- Xaa[13]-Xaa[14]-Maa[15]-Xaa[16]	95
Formula XV	1:6, 2:10, 5:13	Maa[1]-Maa[2]-Glu3-Xaa[4]- Maa[5]-Maa[6]-Asn[7]-Pro[8]-Ala[9]-Maa[10]-Thr[11]-Gly[12]-Maa[13]-Tyr[14]	96
Formula XVI	1:6, 2:10, 5:13	Maa[1]-Maa[2]-Glu3-Xaa[4]- Maa[5]-Maa[6]-Asn[7]-Pro[8]-Ala[9]-Maa[10]-Thr[11]-Gly[12]-Maa[13]-	97
Formula XVII	1:6, 2:10, 5:13	Xaa_{n3}-Maa[1]-Maa[2]-Xaa[3]-Xaa[4]-Maa[5]-Maa[6]-Xaa[7]-Xaa[8]-Xaa[9]-Maa[10]-Xaa[11]-Xaa[12]-Maa[13]-Xaa_{n2}	98

Table III. GCRA Peptides

Name	Position of Disulfide bonds	Structure	SEQ ID NO:
SP-363	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu-AMIDE[16]	99
SP-364	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16]	100
SP-365	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer-AMIDE[16]	101
SP-366	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	102
SP-367	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr-AMIDE[16]	103
SP-373	C4:C12, C7:C15	Pyglu[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu-AMIDE[16]	104
SP-304 di PEG	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]-PEG3	105
SP-304 N-PEG	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	106
SP-304 C-PEG	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]PEG3	107

Table IV. SP-304 Analogs, Uroguanylin , and Uroguanylin Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XVIII	C4:C12, C7:C15	Xaa[1]- Xaa[2]- Xaa[3] -Maa[4]-Xaa[5]-Xaa[6]-Maa[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]-Maa[12]-Xaa[13]-Xaa[14]-Maa[15]-Xaa[16]	108
Uroguanylin	C4:C12, C7:C15	Asn[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]Cys[15]-Leu[16]	109
N32	C4:C12, C7:C15	Glu[1]-Asp[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	110
N33	C4:C12, C7:C15	Glu[1]-Asp[2]-Glu[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	111
N34	C4:C12, C7:C15	Glu[1]-Glu[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	112
N35	C4:C12, C7:C15	Glu[1]-Glu[2]-Glu[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	113
N36	C4:C12, C7:C15	Asp[1]-Asp[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	114
N37	C4:C12, C7:C15	Asp[1]-Asp[2]-Glu[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	115
N38	C4:C12,	Asp[1]-Glu[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	116

	C7:C15		
N39	C4:C12, C7:C15	Asp[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	117
N40	C4:C12, C7:C15	Gln[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	118
N41	C4:C12, C7:C15	Gln[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	119
N42	C4:C12, C7:C15	Gln[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	120
N43	C4:C12, C7:C15	Gln[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	121
N44	C4:C12, C7:C15	Lys[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	122
N45	C4:C12, C7:C15	Lys[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	123
N46	C4:C12, C7:C15	Lys[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	124
N47	C4:C12, C7:C15	Lys[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	125
N48	C4:C12, C7:C15	Glu[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	126
N49	C4:C12, C7:C15	Glu[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	127

N50	C4:C12, C7:C15	Glu[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	128
N51	C4:C12, C7:C15	Glu[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	129
N52	C4:C12, C7:C15	Asp[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	130
N53	C4:C12, C7:C15	Asp[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	131
N54	C4:C12, C7:C15	Asp[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	132
N55	C4:C12, C7:C15	Asp[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	133
N56	C4:C12, C7:C15	Gln[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	134
N57	C4:C12, C7:C15	Gln[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	135
N58	C4:C12, C7:C15	Gln[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	136
N59	C4:C12, C7:C15	Gln[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	137
N60	C4:C12, C7:C15	Lys[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	138
N61	C4:C12,	Lys[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	139

	C7:C15		
N62	C4:C12, C7:C15	Lys[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	140
N63	C4:C12, C7:C15	Lys[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	141
N65	C4:C12, C7:C15	Glu[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	142
N66	C4:C12, C7:C15	Glu[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	143
N67	C4:C12, C7:C15	Glu[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	144
N68	C4:C12, C7:C15	Glu[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	145
N69	C4:C12, C7:C15	Asp[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	146
N70	C4:C12, C7:C15	Asp[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	147
N71	C4:C12, C7:C15	Asp[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	148
N72	C4:C12, C7:C15	Asp[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	149
N73	C4:C12, C7:C15	Gln[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	150

N74	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	151
N75	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	152
N76	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	153
N77	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	154
N78	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	155
N79	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	156
N80	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	157
N81	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	158
N82	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	159
N83	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	160
N84	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	161
N85	C4:C12,	Asp^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	162

	C7:C15		
N86	C4:C12, C7:C15	Asp[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	163
N87	C4:C12, C7:C15	Asp[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	164
N88	C4:C12, C7:C15	Asp[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	165
N89	C4:C12, C7:C15	Gln[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	166
N90	C4:C12, C7:C15	Gln[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	167
N91	C4:C12, C7:C15	Gln[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	168
N92	C4:C12, C7:C15	Gln[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	169
N93	C4:C12, C7:C15	Lys[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	170
N94	C4:C12, C7:C15	Lys[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	171
N95	C4:C12, C7:C15	Lys[1]-Glu[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	172
N96	C4:C12, C7:C15	Lys[1]-Glu[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	173

Table V. Guanylin and Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XIX	4:12,7:15	Xaa^{1}- Xaa^{2}- Xaa^{3} -Maa^{4}-Xaa^{5}-Xaa^{6}-Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Maa^{12}-Xaa^{13}-Xaa^{14}-Maa^{15}	174
Guanylin	C4:C12, C7:C15	Ser^{1}-His^{2}-Thr^{3}-Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Phe^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	175
N97	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	176
N98	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	177
N99	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	178
N100	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	179
N101	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	180
N102	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	181
N103	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	182
N104	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	183
N105	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	184
N106	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	185
N107	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	186

N108	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	187
N109	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	188
N110	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	189
N111	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	190
N112	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	191
N113	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	192
N114	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	193
N115	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	194
N116	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	195
N117	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	196
N118	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	197
N119	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	198
N120	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	199
N121	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	200
N122	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	201
N123	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	202
N124	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	203

N125	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	204
N126	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	205
N127	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	206
N128	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	207

Table VI. Lymphoguanylin and Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XX	4:12,7:15	Xaa^{1}- Xaa^{2}- Xaa^{3} -Maa^{4}-Xaa^{5}-Xaa^{6}-Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Maa^{12}-Xaa^{13}-Xaa^{14}-$Xaa_{n1}{}^{15}$	208
Lymphoguanylin	C4:C12	Gln^{1}-Glu^{2}-Glu-$^{3}Cys^{4}$-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	209
N129	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	210
N130	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	211
N131	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	212
N132	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	213
N133	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	214

N134	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	215
N135	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	216
N136	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	217
N137	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	218
N138	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	219
N139	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	220
N140	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	221
N141	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	222
N142	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	223
N143	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	224
N144	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	225
N145	C4:C12, C7:C15	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	226
N146	C4:C12, C7:C15	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	227
N147	C4:C12, C7:C15	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	228
N148	C4:C12,	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	229

	C7:C15		
N149	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	230
N150	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser	231
N151	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	232
N152	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	233
N153	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	234
N154	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	235
N155	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	236
N156	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	237
N157	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	238

N158	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	239
N159	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	240
N160	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	241

Table VII. ST Peptide and Analogues

Name	Position of Disulfide bonds	Structure	SEQ ID NO
ST Peptide	C3:C8, C4:C12, C7:15	Asn[1]- Ser[2]-Ser[3]-Asn[4]-Ser[5]-Ser[6]-Asn[7]-Tyr[8]-Cys[9]-Cys[10]-Glu[11]-Lys[12]-Cys[13]-Cys[14]-Asn[15]-Pro[16]-Ala[17]-Cys[18]-Thr[19]-Gly[20]-Cys[21]-Tyr[22]	242
N161	C3:C8, C4:C12, C7:15	PEG3-Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	243
N162	C3:C8, C4:C12, C7:15	PEG3-Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	244
N163	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	245
N164	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	246

N165	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	247
N166	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	248
N167	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	249

1.3 Methods of Use

[121] The invention provides methods for treating or preventing gastrointestinal disorders and increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Non-limiting examples of gastrointestinal disorders that can be treated or prevented according to the methods of the invention include irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, constipation associated with use of medications such as opioids, osteoarthritis drugs, or osteoporosis drugs); post surgical constipation, constipation associated with neuropathic disorders, Crohn's disease, and ulcerative colitis.

[122] In one embodiment, the invention provides methods for treating or preventing gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, obesity, congestive heart failure, or benign prostatic hyperplasia.

[123] In one embodiment, the invention provides methods for treating or preventing constipation and/or increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001 Aliment Pharmacol Ther 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of

surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

[124] In various embodiments, the constipation is associated with use of a therapeutic agent; the constipation is associated with a neuropathic disorder; the constipation is postsurgical constipation; the constipation is associated with a gastrointestinal disorder; the constipation is idiopathic (functional constipation or slow transit constipation); the constipation is associated with neuropathic, metabolic or endocrine disorder (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease or cystic fibrosis). Constipation may also be the result of surgery or due to the use of drugs such as analgesics (e.g., opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

[125] In one embodiment, the invention provides methods for treating or preventing chronic idiopathic constipation and increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject.

[126] The term "treating" as used herein refers to a reduction, a partial improvement, amelioration, or a mitigation of at least one clinical symptom associated with the gastrointestinal disorders being treated. The term “preventing” refers to an inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorders to be prevented. The term "effective amount” as used herein refers to an amount that provides some improvement or benefit to the subject. In certain embodiments, an effective amount is an amount that provides some alleviation, mitigation, and/or decrease in at least one clinical symptom of the gastrointestinal disorder to be treated. In other embodiments, the effective amount is the amount that provides some inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorder to be prevented. The therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. The term “subject” preferably refers to a human subject but may also refer to a non-human primate or other mammal preferably selected from among a mouse, a rat, a dog, a cat, a cow, a horse, or a pig.

[127] The invention also provides methods for treating gastrointestinal cancer in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Non-limiting examples of gastrointestinal cancers that can be treated according to the methods of the invention include gastric cancer, esophageal cancer, pancreatic cancer, colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer.

[128] The invention also provides methods for treating lipid metabolism disorders, biliary disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders including cardiovascular disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, and obesity.

[129] Lipid metabolism disorders include, but are not limited to, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, sitosterolemia, familial hypercholesterolemia, xanthoma, combined hyperlipidemia, lecithin cholesterol acyltransferase deficiency, tangier disease, abetalipoproteinemia, erectile dysfunction, fatty liver disease, and hepatitis.

[130] Billary disorders include gallbladder disorders such as for example, gallstones, gall bladder cancer cholangitis, or primary sclerosing cholangitis; or bile duct disorders such as for example,cholecystitis, bile duct cancer or fascioliasis.

[131] Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (e.g., nephritis), gastrointestinal system inflammation (e.g., Crohn's disease and ulcerative colitis); necrotizing enterocolitis (NEC); pancreatic inflammation (e.g., pancreatis), lung inflammation (e.g., bronchitis or asthma) or skin inflammation (e.g., psoriasis, eczema).

[132] Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis.

[133] Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer, (e.g., gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (e.g., melanoma); oral cancer; urinary tract cancer (e.g. bladder cancer or kidney cancer); blood cancer (e.g. myeloma or leukemia) or prostate cancer.

[134] Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high triglycerides. Cardiovascular disorders include for example aneurysm, angina, atherosclerosis, cerebrovascular accident (stroke), cerebrovasculardisease, congestive heart failure, coronary artery disease, myocardial infarction (heart attack), or peripheral vascular disease.

[135] Liver disorders include for example cirrhosis and fibrosis. In addition, GC-C agonist may also be useful to facilitate liver regeneration in liver transplant patients. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (e.g., periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

1.3.1 Therapeutically Effective Dosages

[136] Disorders are treated, prevented or alleviated by administering to a subject, *e.g.*, a mammal such as a human in need thereof, a therapeutically effective dose of a GCC agonist peptide. The present invention is based in part on the unexpected results of clinical trials in humans which demonstrated that the formulations of the invention are therapeutically effective at much lower doses than predicted based on animal studies. In accordance with one aspect of the invention, the therapeutically effective dose is between 0.01 milligrams (mg) and 10 mg per unit dose. The term “unit dose” refers to a single drug delivery entity, *e.g.*, a tablet, capsule, solution or inhalation formulation. In one embodiment, the effective dose is between 0.01 mg and 9 mg. In another embodiment, the effective dose is between 0.01 mg and 5 mg. In another embodiment, the effective dose is between 0.01 mg and 3 mg. In another embodiment, the effective dose is between 0.10 mg and 5 mg. In another embodiment, the effective dose is between 0.10 mg and 3 mg. In one embodiment, the unit dose is .01 mg, .05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 5 mg, or 10 mg. In one embodiment, the unit dose is 0.3 mg, 1.0 mg, 3.0 mg, 9.0 mg, or 9.5 mg.

[137] The GCC agonist peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient. What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art.

[138] The GCC agonists for use in the methods described above are preferably administered orally. Dosage forms include solutions, suspensions, emulsions, tablets, and capsules.

[139] The total daily dose can be administered to the patient in a single dose, or in multiple sub-doses. Typically, sub-doses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Preferably, a single daily dose is administered.

[140] The GCC agonists may be administered as either the sole active agent or in combination with one or more additional active agents. In all cases, additional active agents should be administered at a dosage that is therapeutically effective using the existing art as a guide. The GCC agonists may be administered in a single composition or sequentially with the one or more additional active agents. In one embodiment, the GCC agonist is administered in combination with one or more inhibitors of cGMP dependent phosphodiesterase such as suldinac sulfone, zaprinast, motapizone, vardenafil, or sildenifil. In another embodiment, the GCC agonist is administered in combination with one or more chemotherapeutic agents. In another embodiment, the GCC agonist is administered in combination with one or more or anti-inflammatory drugs such as steroids or non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin.

[141] Combination therapy can be achieved by administering two or more agents, *e.g.*, a GCC agonist peptide described herein and another compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a

third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[142] The GCC agonist peptides described herein may be combined with phosphodiesterase inhibitors, *e.g.*, sulindae sulfone, Zaprinast, sildenafil, vardenafil or tadalafil to further enhance levels of cGMP in the target tissues or organs.

[143] Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, *e.g.*, in the order X-Y- X, X-X-Y, Y-X-Y,Y-Y-X,X-X-Y-Y, etc.

1.3.2 Exemplary Agents for Combination Therapy

[144] The GCC agonist formulations of the invention may be administered alone or in combination with one or more additional therapeutic agents as part of a therapeutic regimen for the treatment or prevention of a gastrointestinal disease or disorder. In some embodiments, the GCC agonist formulation comprises one or more additional therapeutic agents. In other embodiments, the GCC agonist is formulated separately from the one or more additional therapeutic agents. In accordance with this embodiment, the GCC agonist is administered either simultaneously, sequentially, or at a different time than the one or more additional therapeutic agents. In one embodiment, the GCC agonist formulation is administered in combination with one or more additional therapeutic agents selected from the group consisting of phosphodiesterase inhibitors, cyclic nucleotides (such as cGMP and cAMP), a laxative (such as SENNA or METAMUCIL), a stool softner, an anti-tumor necrosis factor alpha therapy for IBD

(such as REMICADE, ENBREL, or HUMIRA), and anti-inflammatory drugs (such as COX-2 inhibitors, sulfasalazine, 5-ASA derivatives and NSAIDS). In certain embodiments, the GCC agonist formulation is administered in combination with an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said GCC agonist. cGMP-PDE inhibitors include, for example, suldinac sulfone, zaprinast, motapizone, vardenifil, and sildenafil. In another embodiment, the GCC agonist formulation is administered in combination with inhibitors of cyclic nucleotide transporters. Further examples of therapeutic agents that may be administered in combination with the GCC agonist formulations of the invention are given in the following sections.

1.3.2.1 Agents to Treat Gastrointestinal Cancers

[145] The GCC agonist formulations described herein can be used in combination with one or more antitumor agents including but not limited to alkylating agents, epipodophyllotoxins, nitrosoureas, anti-metabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular antitumor agents include tamoxifen, taxol, etoposide, and 5-fluorouracil. In one embodiment, the GCC agonist formulations are used in combination with an antiviral agent or a monoclonal antibody.

[146] Non-limiting examples of antitumor agents that can be used in combination with the GCC agonist formulations of the invention for the treatment of colon cancer include anti-proliferative agents, agents for DNA modification or repair, DNA synthesis inhibitors, DNA/RNA transcription regulators, RNA processing inhibitors, agents that affect protein expression, synthesis and stability, agents that affect protein localization or their ability to exert their physiological action, agents that interfere with protein-protein or protein-nucleic acid interactions, agents that act by RNA interference, receptor binding molecules of any chemical nature (including small molecules and antibodies), targeted toxins, enzyme activators, enzyme inhibitors, gene regulators, HSP-90 inhibitors, molecules interfering with microtubules or other cytoskeletal components or cell adhesion and motility, agents for phototherapy, and therapy adjuncts.

[147] Representative anti-proliferative agents include N-acetyl-D-sphingosine (C.sub.2 ceramide), apigenin, berberine chloride, dichloromethylenediphosphonic acid disodium salt, loe-emodine, emodin, HA 14-1, N-hexanoyl-D-sphingosine (C.sub.6 ceramide), 7b-hydroxycholesterol, 25-hydroxycholesterol, hyperforin, parthenolide, and rapamycin.

Representative agents for DNA modification and repair include aphidicolin, bleomycin sulfate, carboplatin, carmustine, chlorambucil, cyclophosphamide monohydrate, cyclophosphamide monohydrate ISOPAC.RTM., cis-diammineplatinum(II) dichloride (Cisplatin), esculetin, melphalan, methoxyamine hydrochloride, mitomycin C, mitoxantrone dihydrochloride, oxaliplatin, and streptozocin.

[148] Representative DNA synthesis inhibitors include (.+-.)amethopterin (methotrexate), 3-amino-1,2,4-benzotriazine 1,4-dioxide, aminopterin, cytosine b-D-arabinofurdnoside (Ara-C), cytosine b-D-arabinofuranoside (Ara-C) hydrochloride, 2-fluoroadenine-9-b-D-arabinofuranoside (Fludarabine des-phosphate; F-ara-A), 5-fluoro-5'-deoxyuridinc, 5-fluorouracil, ganciclovir, hydroxyurea, 6-mercaptopurine, and 6-thioguanine.

[149] Representative DNA/RNA transcription regulators include actinomycin D, daunorubicin hydrochloride, 5,6-dichlorobenzimidazole 1-b-D-ribofuranoside, doxorubicin hydrochloride, homoharringtonine, and idarubicin hydrochloride.

[150] Representative enzyme activators and inhibitors include forskolin, DL-aminoglutethimide, apicidin, Bowman-Birk Inhibitor, butein, (S)-(+)-camptothecin, curcumin, (-)-deguelin, (-)-depudecin, doxycycline hyclate, etoposide, formestane, fostriecin sodium salt, hispidin, 2-imino-1-imidazolidineacetic acid (Cyclocreatine), oxamflatin, 4-phenylbutyric acid, roscovitine, sodium valproate, trichostatin A, tyrphostin AG 34, tyrphostin AG 879, urinary trypsin inhibitor fragment, valproic acid (2-propylpentanoic acid), and XK469.

[151] Representative gene regulators include 5-aza-2'-deoxycytidine, 5-azacytidine, cholecalciferol (Vitamin D3), ciglitizone, cyproterone acetate, 15-deoxy-D.sup.12,14-prostaglandin J.sub.2, epitestosterone, flutamide, glycyrrhizic acid ammonium salt (glycyrrhizin), 4-hydroxytamoxifen, mifepristone, procainamide hydrochloride, raloxifene hydrochloride, all trans-retinal (vitamin A aldehyde), retinoic acid (vitamin A acid), 9-cis-

retinoic acid, 13-cis-retinoic acid, retinoic acid p-hydroxyanilide, retinol (Vitamin A), tamoxifen, tamoxifen citrate salt, tetradecylthioacetic acid, and troglitazone.

[152] Representative HSP-90 inhibitors include 17-(allylamino)-17-demethoxygeldanamycin and geldanamycin.

[153] Representative microtubule inhibitors include colchicines, dolastatin 15, nocodazole, taxanes and in particular paclitaxel, podophyllotoxin, rhizoxin, vinblastine sulfate salt, vincristine sulfate salt, and vindesine sulfate salt and vinorelbine (Navelbine) ditartrate salt.

[154] Representative agents for performing phototherapy include photoactive porphyrin rings, hypericin, 5-methoxypsoralen, 8-methoxypsoralen, psoralen and ursodeoxycholic acid.

[155] Representative agents used as therapy adjuncts include amifostine, 4-amino-1,8-naphthalimide, brefeldin A, cimetidine, phosphomycin disodium salt, leuprolide (leuprorelin) acetate salt, luteinizing hormone-releasing hormone (LH-RH) acetate salt, lectin, papaverine hydrochloride, pifithrin-a, (-)-scopolamine hydrobromide, and thapsigargin.

[156] The agents can also be anti-VEGF (vascular endothelial growth factor) agents, as such are known in the art. Several antibodies and small molecules are currently in clinical trials or have been approved that function by inhibiting VEGF, such as Avastin (Bevacizumab), SU5416, SU11248 and BAY 43-9006. The agents can also be directed against growth factor receptors such as those of the EGF/Erb-B family such as EGF Receptor (Iressa or Gefitinib, and Tarceva or Erlotinib), Erb-B2, receptor (Herceptin or Trastuzumab), other receptors (such as Rituximab or Rituxan/MabThera), tyrosine kinases, non-receptor tyrosine kinases, cellular serine/threonine kinases (including MAP kinases), and various other proteins whose deregulation contribute to oncogenesis (such as small/Ras family and large/heterotrimeric G proteins). Several antibodies and small molecules targeting those molecules are currently at various stages of development (including approved for treatment or in clinical trials).

[157] In a preferred embodiment, the invention provides a method for treating colon cancer in a subject in need thereof by administering to the subject a GCC agonist formulation in combination with one or more antitumor agent selected from the group consisting of paclitaxel,

docetaxel, tamoxifen, vinorelbine, gemcitabine, cisplatin, etoposide, topotecan, irinotecan, anastrozole, rituximab, trastuzumab, fludarabine, cyclophosphamide, gentuzumab, carboplatin, interferons, and doxorubicin. In a particular embodiment the antitumor agent is paclitaxel. In a further embodiment, the method further comprises an antitumor agent selected from the group consisting of 5-FU, doxorubicin, vinorelbine, cytoxan, and cisplatin.

1.3.2.2 Agents that Treat Crohn's Disease

[158] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of Crohn's disease. Non-limiting examples of the one or more additional therapeutic agents include sulfasalazine and other mesalamine-containing drugs, generally known as 5-ASA agents, such as Asacol, Dipentum, or Pentasa, or infliximab (REMICADE). In certain embodiments, the one or more additional agents is a corticosteroid or an immunosuppressive agent such as 6-mercaptopurine or azathioprine. In another embodiment, the one or more additional agents is an antidiarrheal agent such as diphenoxylate, loperamide, or codeine.

1.3.2.3 Agents that Treat Ulcerative Colitis

[159] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of ulcerative colitis. The agents that are used to treat ulcerative colitis overlap with those used to treat Chrohn's Disease. Non-limiting examples of the one or more additional therapeutic agents that can be used in combination with a GCC agonist formulation of the invention include aminosalicylates (drugs that contain 5-aminosalicyclic acid (5-ASA)) such as sulfasalazine, olsalazine, mesalamine, and balsalazide. Other therapeutic agents that can be used include corticosteroids, such as prednisone and hydrocortisone, immunomodulators, such as azathioprine, 6-mercapto-purine (6-MP), cytokines, interleukins, and lymphokines, and anti-TNF-alpha agents, including the thiazolidinediones or glitazones such as rosiglitazone and pioglitazone. In one emobidment, the one or more additional therapeutic agents includes both cyclosporine A and 6-MP or azathioprine for the treatment of active, severe ulcerative colitis.

1.3.2.4 Agents that Treat Constipation/Irritable Bowel Syndrome

[160] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of constipation, such as that associated with irritable bowel syndrome. Non-limiting examples of the one or more additional therapeutic agents include laxatives such as SENNA, MIRALAX, LACTULOSE, PEG, or calcium polycarbophil), stool softeners (such as mineral oil or COLACE), bulking agents (such as METAMUCIL or bran), agents such as ZELNORM (also called tegaserod), and anticholinergic medications such as BENTYL and LEVSIN.

1.3.2.5 Agents for the Treatment of Postoperative Ileus

[161] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of postoperative ileus. Non-limiting examples of the one or more additional therapeutic agents include ENTEREG (alvimopan; formerly called ado lor/ ADL 8-2698), conivaptan, and related agents describes in US 6,645,959.

1.3.2.6 Anti-obesity agents

[162] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of obesity. Non-limiting examples of the one or more additional therapeutic agents include 1 lβ HSD-I (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498, BVT 2733, 3-(l-adamantyl)-4-ethyl-5-(ethylthio)- 4H-l,2,4-triazole, 3-(l-adamantyl)-5-(3,4,5-trimethoxyphenyl)-4-methyl-4H-l,2,4-triazole, 3- adamantanyl-4,5,6,7,8,9,10,11,12,3a-decahydro-l,2,4-triazolo[4,3-a][l l]annulene, and those compounds disclosed in WO01/90091, WOO 1/90090, WOO 1/90092 and WO02/072084; 5HT antagonists such as those in WO03/037871, WO03/037887, and the like; 5HTIa modulators such as carbidopa, benserazide and those disclosed in US6207699, WO03/031439, and the like; 5HT2c (serotonin receptor 2c) agonists, such as BVT933, DPCA37215, IK264, PNU 22394, WAY161503, R-1065, SB 243213 (Glaxo Smith Kline) and YM 348 and those disclosed in US3914250, WO00/77010,

WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457; 5HT6 receptor modulators, such as those in WO03/030901, WO03/035061, WO03/039547, and the like; acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al, Obesity Research, 9:202-9 (2001) and Japanese Patent Application No. JP 2000256190; anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO00/18749, WO01/32638, WO01/62746, WO01/62747, and WO03/015769; CB 1 (cannabinoid-1 receptor) antagonist/inverse agonists such as rimonabant (Acomplia; Sanofi), SR-147778 (Sanofi), SR-141716 (Sanofi), BAY 65-2520 (Bayer), and SLV 319 (Solvay), and those disclosed in patent publications US4973587, US5013837, US5081122, US5112820, US5292736, US5532237, US5624941, US6028084, US6509367, US6509367, WO96/33159, WO97/29079, WO98/31227, WO98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO01/09120, WO01/58869, WO01/64632, WO01/64633, WO01/64634, WO01/70700, WO01/96330, WO02/076949, WO03/006007, WO03/007887, WO03/020217, WO03/026647, WO03/026648, WO03/027069, WO03/027076, WO03/027114, WO03/037332, WO03/040107, WO03/086940, WO03/084943 and EP658546; CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771 (GSK), JMV-180, A- 71378, A-71623 and SR146131 (Sanofi), and those described in US5739106; CNTF (Ciliary neurotrophic factors), such as GI- 181771 (Glaxo-SmithKline), SRl 46131 (Sanofi Synthelabo), butabindide, PD 170,292, and PD 149164 (Pfizer); CNTF derivatives, such as Axokine® (Regeneron), and those disclosed in WO94/09134, WO98/22128, and WO99/43813; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, P 3298, TSL 225 (tryptophyl-l,2,3,4-tetrahydroisoquinoline-3- carboxylic acid; disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), TMC-2A/2B/2C, CD26 inhibtors, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, 2- cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) and the compounds disclosed patent publications. WO99/38501, WO99/46272, WO99/67279 (Probiodrug), WO99/67278 (Probiodrug), WO99/61431 (Probiodrug), WO02/083128, WO02/062764, WO03/000180, WO03/000181, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/004498, WO03/004496,WO03/017936, WO03/024942,

WO03/024965, WO03/033524, WO03/037327 and EP1258476; growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK- 0677 (Merck), SM-130686, CP-424391 (Pfizer), LY 444,711 (Eli Lilly), L-692,429 and L- 163,255, and such as those disclosed in USSN 09/662448, US provisional application 60/203335, US6358951, US2002049196, US2002/022637, WO01/56592 and WO02/32888; H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(lH-imidazol-4- yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, O-[3-(lH-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N- phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO02/15905, WO03/024928 and WO03/024929; leptin derivatives, such as those disclosed in US5552524, US5552523, US5552522, US5521283, WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520; leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); lipase inhibitors, such as tetrahydrolipstatin (orlistat/Xenical®), Triton WRl 339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in patent publications WO01/77094, US4598089, US4452813, USUS5512565, US5391571, US5602151, US4405644, US4189438, and US4242453; lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO03/011267; Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME- 10142, ME-10145, and HS-131 (Melacure), and those disclosed in PCT publication Nos. WO99/64002, WO00/74679, WOO 1/991752, WOO 1/25192, WOO 1/52880, WOO 1/74844, WOO 1/70708, WO01/70337, WO01/91752, WO02/059095, WO02/059107, WO02/059108, WO02/059117, WO02/06276, WO02/12166, WO02/11715, WO02/12178, WO02/15909, WO02/38544, WO02/068387, WO02/068388, WO02/067869, WO02/081430, WO03/06604, WO03/007949, WO03/009847, WO03/009850, WO03/013509,

and WO03/031410; Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO97/19952, WO00/15826, WO00/15790, US20030092041; melanin-concentrating hormone 1 receptor (MCHR) antagonists, such as T-226296 (Takeda), SB 568849, SNP-7941 (Synaptic), and those disclosed in patent publications WOO 1/21169, WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, WO03/13574, WO03/15769, WO03/028641, WO03/035624, WO03/033476, WO03/033480, JP13226269, and JP1437059; mGluR5 modulators such as those disclosed in WO03/029210, WO03/047581, WO03/048137, WO03/051315, WO03/051833, WO03/053922, WO03/059904, and the like; serotoninergic agents, such as fenfluramine (such as Pondimin® (Benzeneethanamine, N-ethyl- alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Robbins), dexfenfluramine (such as Redux® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Interneuron) and sibutramine ((Meridia®, Knoll/Reductil™) including racemic mixtures, as optically pure isomers (+) and (-), and pharmaceutically acceptable salts, solvents, hydrates, clathrates and prodrugs thereof including sibutramine hydrochloride monohydrate salts thereof, and those compounds disclosed in US4746680, US4806570, and US5436272, US20020006964, WOO 1/27068, and WOO 1/62341; NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; NPY 1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI- 264879A, and those disclosed in US6001836, WO96/14307, WO01/23387, WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528; NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, GW-569180A, GW-594884A, GW- 587081X, GW-548118X, FR235208, FR226928, FR240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY-366377, PD-160170, SR- 120562A, SR-120819A, JCF-104, and H409/22 and those compounds disclosed in patent publications US6140354, US6191160, US6218408, US6258837, US6313298, US6326375, US6329395, US6335345, US6337332, US6329395, US6340683, EP01010691, EP-01044970, WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO/0113917, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/02379, WO01/23388, WO01/23389, WOO 1/44201, WO01/62737, WO01/62738, WO01/09120,

WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/051806, WO02/094789, WO03/009845, WO03/014083, WO03/022849, WO03/028726 and Norman et al, J. Med. Chem. 43:4288-4312 (2000); opioid antagonists, such as nalmefene (REVEX ®), 3-methoxynaltrexone, methylnaltrexone, naloxone, and naltrexone (e.g. PT901; Pain Therapeutics, Inc.) and those disclosed in US20050004155 and WO00/21509; orexin antagonists, such as SB-334867-A and those disclosed in patent publications WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847; PDE inhibitors (e.g. compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and cGMP; possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors) such as those disclosed in patent publications DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOl 12987, EPOl 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, US4963561, US5141931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926,

WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEl 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6331543, US20050004222 (including those disclosed in formulas I- XIII and paragraphs 37-39, 85-0545 and 557-577), WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399, as well as PDE5 inhibitors (such as RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra™)), PDE4 inhibitors (such as etazolate, ICI63197, RP73401, imazolidinone (RO-20-1724), MEM 1414 (R1533/R1500; Pharmacia Roche), denbufylline, rolipram, oxagrelate, nitraquazone, Y-590, DH-6471, SKF-94120, motapizone, lixazinone, indolidan, olprinone, atizoram, KS-506-G, dipamfylline, BMY-43351, atizoram, arofylline, filaminast, PDB-093, UCB-29646, CDP-840, SKF-107806, piclamilast, RS-17597, RS-25344- 000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, mopidamol, anagrelide, ibudilast, amrinone, pimobendan, cilostazol, quazinone and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide, PDE3 inhibitors (such as ICI153, 100, bemorandane (RWJ 22867), MCI-154, UD-CG 212, sulmazole, ampizone, cilostamide, carbazeran, piroximone, imazodan, CI-930, siguazodan, adibendan, saterinone, SKF-95654, SDZ-MKS-492, 349-U-85, emoradan, EMD-53998, EMD- 57033, NSP-306, NSP-307, revizinone, NM-702, WIN-62582 and WIN-63291, enoximone and milrinone, PDE3/4 inhibitors (such as benafentrine, trequinsin, ORG-30029, zardaverine, L- 686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and tolafentrine) and other PDE inhibitors (such as vinpocetin, papaverine, enprofylline, cilomilast, fenoximone, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®); Neuropeptide Y2 (NPY2) agonists include but are not limited to: polypeptide YY and fragments and variants thereof (e.g. YY3-36 (PYY3-36)(N. Engl. J. Med. 349:941, 2003; IKPEAPGE DASPEELNRY YASLRHYLNL VTRQRY (SEQ ID NO:XXX)) and PYY agonists such as those disclosed in WO02/47712, WO03/026591, WO03/057235, and WO03/027637; serotonin reuptake inhibitors, such as, paroxetine, fluoxetine (Prozac™), fluvoxamine, sertraline, citalopram, and imipramine, and those disclosed in US6162805, US6365633, WO03/00663, WOO 1/27060, and WOO 1/162341; **thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in** WO02/15845, WO97/21993, WO99/00353, GB98/284425, U.S. Provisional Application No.

60/183,223, and Japanese Patent Application No. JP 2000256190; UCP-I (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5, 6,7,8- tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-l-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in WO99/00123; β3 (beta adrenergic receptor 3) agonists, such as AJ9677/TAK677 (Dainippon/Takeda), L750355 (Merck), CP331648 (Pfizer), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), SR 59119A, and those disclosed in US5541204, US5770615, US5491134, US5776983, US488064, US5705515, US5451677, WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881; noradrenergic agents including, but not limited to, diethylpropion (such as Tenuate® (1- propanone, 2-(diethylamino)-l -phenyl-, hydrochloride), Merrell), dextroamphetamine (also known as dextroamphetamine sulfate, dexamphetamine, dexedrine, Dexampex, Ferndex, Oxydess II, Robese, Spancap #1), mazindol ((or 5-(p-chlorophenyl)-2,5-dihydro-3H- imidazo[2,l-a]isoindol-5-ol) such as Sanorex®, Novartis or Mazanor®, Wyeth Ayerst), phenylpropanolamine (or Benzenemethanol, alpha-(l-aminoethyl)-, hydrochloride), phentermine ((or Phenol, 3-[[4,5-duhydro-lH-imidazol-2-yl)ethyl](4-methylpheny-l)amino], monohydrochloride) such as Adipex-P®, Lemmon, FASTIN®, Smith-Kline Beecham and Ionamin®, Medeva), phendimetrazine ((or (2S,3S)-3,4-Dimethyl-2phenylmorpholine L-(+)- tartrate (1 :1)) such as Metra® (Forest) , Plegine® (Wyeth- Ay erst), Prelu-2® (Boehringer Ingelheim), and Statobex® (Lemmon), phendamine tartrate (such as Thephorin® (2,3,4,9- Tetrahydro-2-methyl-9-phenyl-lH-indenol[2,l-c]pyridine L-(+)-tartrate (1 :1)), Hoffmann- LaRoche), methamphetamine (such as Desoxyn®, Abbot ((S)-N, (alpha)-dimethylbenzeneethanamine hydrochloride)), and phendimetrazine tartrate (such as Bontril® Slow-Release Capsules, Amarin (-3,4-Dimethyl-2-phenylmorpholine Tartrate); fatty acid oxidation upregulator/inducers such as Famoxin® (Genset); monamine oxidase inhibitors including but not limited to befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide, caroxazone and other certain compounds as disclosed by WO01/12176; and other anti-obesity agents such as 5HT-2 agonists, ACC (acetyl-CoA carboxylase) inhibitors such as those described

in WO03/072197, alpha-lipoic acid (alpha-LA), AOD9604, appetite suppressants such as those in WO03/40107, ATL-962 (Alizyme PLC), benzocaine, benzphetamine hydrochloride (Didrex), bladderwrack (focus vesiculosus), BRS3 (bombesin receptor subtype 3) agonists, bupropion, caffeine, CCK agonists, chitosan, chromium, conjugated linoleic acid, corticotropin-releasing hormone agonists, dehydroepiandrosterone, DGATl (diacylglycerol acyltransferase 1) inhibitors, DGAT2 (diacylglycerol acyltransferase 2) inhibitors, dicarboxylate transporter inhibitors, ephedra, exendin-4 (an inhibitor of glp-1) FAS (fatty acid synthase) inhibitors (such as Cerulenin and C75), fat resorption inhibitors (such as those in WO03/053451, and the like), fatty acid transporter inhibitors, natural water soluble fibers (such as psyllium, plantago, guar, oat, pectin), galanin antagonists, galega (Goat's Rue, French Lilac), garcinia cambogia, germander (teucrium chamaedrys), ghrelin antibodies and ghrelin antagonists (such as those disclosed in WO01/87335, and WO02/08250), polypeptide hormones and variants thereof which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory polypeptide (GIP)/vasoactive intestinal polypeptide (VIP)/pituitary adenylate cyclase activating polypeptide (PACAP)/glucagon-like polypeptide II (GLP- II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related polypeptide (CGRP) gene family includingGLP-1 (glucagon- like polypeptide 1) agonists (e.g. (1) exendin-4, (2) those GLP-I molecules described in US20050130891 including GLP- 1(7-34), GLP-l(7-35), GLP-l(7-36) or GLP-l(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-I polypeptides and modifications thereof including those described in paragraphs 17-44 of US20050130891, and derivatives derived from GLP-l-(7- 34)COOH and the corresponding acid amide are employed which have the following general formula: R-NH-HAEGTFTSDVSYLEGQAAKEFIAWLVK-$CONH_2$ wherein R=H or an organic compound having from 1 to 10 carbon atoms. Preferably, R is the residue of a carboxylic acid. Particularly preferred are the following carboxylic acid residues: formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert- butyl.) and glp-1 (glucagon-like polypeptide- 1), glucocorticoid antagonists, glucose transporter inhibitors, growth hormone secretagogues (such as those disclosed and specifically described in US5536716), interleukin-6 (IL-6) and modulators thereof (as in WO03/057237, and the like), L- carnitine, Mc3r (melanocortin 3 receptor) agonists, MCH2R (melanin concentrating hormone 2R)

agonist/antagonists, melanin concentrating hormone antagonists, melanocortin agonists (such as Melanotan II or those described in WO 99/64002 and WO 00/74679), nomame herba, phosphate transporter inhibitors, phytopharm compound 57 (CP 644,673), pyruvate, SCD-I (stearoyl-CoA desaturase-1) inhibitors, T71 (Tularik, Inc., Boulder CO), Topiramate (Topimax®, indicated as an anti-convulsant which has been shown to increase weight loss), transcription factor modulators (such as those disclosed in WO03/026576), β-hydroxy steroid dehydrogenase- 1 inhibitors (β -HSD-I), β-hydroxy-β-methylbutyrate, p57 (Pfizer), Zonisamide (Zonegran™, indicated as an anti-epileptic which has been shown to lead to weight loss), and the agents disclosed in US20030119428 paragraphs 20-26.

1.3.2.7 Phosphodiesterase inhibitors

[163] In certain embodiments, the regimen of combination therapy includes the administration of one or more phosphodiesterase ("PDE") inhibitors. PDE inhibitors slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibiting phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and/or cGMP. Non-limiting examples of PDE inhibitors that can be used in combination with the GCC agonists of the invention include PDE3 inhibitors, PDE4 inhibitors and/or PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors. Non-limiting examples of such PDE inhibitors are described in the following patent applications and patents: DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOl 12987, EPOl 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, U.S. Pat. Nos. 4,963,561, 5,141,931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024,

WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEl 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6,331,543, US20050004222 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577) and WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399. PDE5 inhibitors which may be mentioned by way of example are RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra®). PDE4 inhibitors which may be mentioned by way of example are RO-20-1724, MEM 1414 (R1533/R1500; Pharmacia Roche), DENBUFYLLINE, ROLIPRAM, OXAGRELATE, NITRAQUAZONE, Y-590, DH-6471, SKF-94120, MOTAPIZONE, LIXAZINONE, INDOLIDAN, OLPRINONE, ATIZORAM, KS-506-G, DIPAMFYLLINE, BMY-43351, ATIZORAM, AROFYLLINE, FILAMINAST, PDB-093, UCB-29646, CDP-840, SKF- 107806, PICLAMILAST, RS- 17597, RS-25344-000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, MOPIDAMOL, ANAGRELIDE, IBUDILAST, AMRINONE, PIMOBENDAN, CILOSTAZOL, QUAZINONE and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide. PDE3 inhibitors which may be mentioned by way of example are SULMAZOLE, AMPIZONE, CILOSTAMIDE, CARBAZERAN, PIROXIMONE, IMAZODAN, CI-930, SIGUAZODAN, ADIBENDAN, SATERINONE, SKF-95654, SDZ-MKS-492, 349-U-85, EMORADAN, EMD-53998, EMD-57033, NSP-306, NSP-307, REVIZINONE, NM-702, WIN-62582 and WIN-63291, ENOXIMONE and MILRINONE. PDE3/4 inhibitors which may be mentioned by way of example are BENAFENTRINE, TREQUINSIN, ORG-30029, ZARDAVERINE, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and TOLAFENTRINE. Other PDE inhibitors include: **cilomilast, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®),** zaprinast (PDE5 specific). GCC AGONIST

1.3.2.8 Analgesic Agents

[164] In certain embodiments, the regimen of combination therapy includes the administration of one or more analgesic agents, *e.g.*, an analgesic compound or an analgesic polypeptide. In some embodiments, the GCC agonist formulation is administered simultaneously or sequentially with one or more analgesic agents. In other embodiments, the GCC agonist is covalently linked or attached to an analgesic agent to create a therapeutic conjugate. Non-limiting examples of analgesic agents that can be used include calcium channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HTl receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NKl receptor antagonists, CCK receptor agonists (*e.g.*, loxiglumide), NKl receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Further examples of analgesic agents in the various classes are known in the art.

[165] In one embodiment, the analgesic agent is an analgesic polypeptide selected from the group consisting of sialorphin-related polypeptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO: 239), including: VQHNPR (SEQ ID NO: 240); VRQHNPR (SEQ ID NO: 241); VRGQHNPR (SEQ ID NO: 242); VRGPQHNPR (SEQ ID NO: 243); VRGPRQHNPR (SEQ ID NO: 244); VRGPRRQHNPR (SEQ ID NO: 245); and RQHNPR (SEQ ID NO: 246). Sialorphin-related polypeptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or polypeptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the GCC agonists described herein or covalently linked to a GCC agonist to form a therapeutic conjugate. Sialorphin and related polypeptides are described in U.S. Patent 6,589,750; U.S. 20030078200 Al; and WO 02/051435 A2.

[166] In another embodiment, a GCC agonist formulation of the invention is administered as part of a regimen of combination therapy with an opioid receptor antagonist or agonist. In one embodiment, the GCC agonist and the opioid receptor antagonist or agonist are linked via a covalent bond. Non-limiting examples of opioid receptor antagonists include naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, nor-binaltorphimine, enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-

homoserine), trimebutine, vasoactive intestinal polypeptide, gastrin, glucagons. Non-limiting examples of opioid receptor agonists include fedotozine, asimadoline, and ketocyclazocine, the compounds described in WO03/097051 and WO05/007626, morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH 2; WO 01/019849 Al), and loperamide.

[167] Further non-limiting examples of analgesic agents that can be used in a regimen of combination therapy along with the GCC agonist formulations of the invention include the dipeptide Tyr-Arg (kyotorphin); the chromogranin-derived polypeptide (CgA 47-66; *See, e.g.*, Ghia et al. 2004 Regulatory polypeptides 119:199); CCK receptor agonists such as caerulein; conotoxin polypeptides; peptide analogs of thymulin (FR Application 2830451); CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R- isomer of loxiglumide) (WO 88/05774); 5-HT4 agonists such as tegaserod (Zelnorm®), mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirexapride; calcium channel blockers such as ziconotide and related compounds described in, for example, EP625162B1, US 5,364,842, US 5,587,454, US 5,824,645, US 5,859,186, US 5,994,305, US 6087,091, US 6,136,786, WO 93/13128 Al, EP 1336409 Al, EP 835126 Al, EP 835126 Bl, US 5,795,864, US 5,891,849, US 6,054,429, WO 97/01351 Al; NK-I, receptor antagonists such as aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-48968 (Sanofi Synthelabo), CP-122,721 (Pfizer, Inc.), GW679769 (Glaxo Smith Kline), TAK-637 (Takeda/Abbot), SR-14033, and related compounds described in, for example, EP 873753 Al, US 20010006972 Al, US 20030109417 Al, WO 01/52844 Al (for a review see Giardina et al. 2003.Drugs 6:758); NK-2 **receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), GW597599 (Glaxo Smith Kline), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc); NK3 receptor antagonists such as osanetant (SR-142801; Sanofi-Synthelabo), SSR-**241586, talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 Al, WO 97/21680 Al, US 6,277,862, WO 98/1 1090, WO 95/28418, WO 97/19927, and Boden et al. (J Med Chem. 39:1664-75, 1996); norepinephrine-serotonin reuptake inhibitors (NSRI) such as milnacipran and related compounds described in WO 03/077897; and vanilloid receptor antagonists such as arvanil and related compouds described in WO 01/64212 Al.

[168] In addition to sialorphin-related polypeptides, analgesic polypeptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, ziconotide, and substance P.

1.3.2.9 Insulin and Insulin Modulating Agents

[169] The GCC agonist peptides described herein can be used in combination therapy with insulin and related compounds including primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form. Sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin). See, the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins).

[170] The GCC peptides described herein can also be used in combination therapy with agents that can boost insulin effects or levels of a subject upon administration, e.g. glipizide and/or rosiglitazone. The polypeptides and agonistsdescribed herein can be used in combitherapy with SYMLIN® (pramlintide acetate) and Exenatide® (synthetic exendin-4; a 39 aa polypeptide).

1.3.2.10 Anti-Hypertensive Agents

[171] The GCC agonist peptides described herein can be used in combination therapy with an anti-hypertensive agent including but not limited to: (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; carbonic anhydrase inhibitors, osmotics(such as glycerin) and aldosterone antagonists, such as spironolactone, epirenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine,

nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; ceranapril; cilazapril; delapril; enalapril; enalopril; fosinopril; imidapril; lisinopril; losinopril; moexipril; quinapril; quinaprilat; ramipril; perindopril; perindropril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril and ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol, and the like; (8) angiotensin II receptor antagonists such as aprosartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, pratosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, **and RNH6270, and the like; (9) α/β adrenergic blockers such as nipradilol, arotinolol and** amosulalol, and the like; (10) alpha 1 blockers, such as terazosin, urapidil, prazosin, tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, and XENOlO, and the like; (11) alpha 2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; (12) aldosterone inhibitors, and the like; and (13) angiopoietin-2 -binding agents such as those disclosed in WO03/030833. Specific anti-hypertensive agents that can be used in combination with polypeptides and agonists described herein include, but are not limited to: diuretics, such as thiazides (e.g., chlorthalidone, cyclothiazide (CAS RN 2259-96-3), chlorothiazide (CAS RN 72956-09-3, which may be prepared as disclosed in US2809194), dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, bendroflumethazide, methyclothazide, polythiazide, trichlormethazide, chlorthalidone, indapamide, metolazone, quinethazone, althiazide (CAS RN 5588-16-9, which may be prepared as disclosed in British Patent No. 902,658), benzthiazide (CAS RN 91-33-8, which may be prepared as disclosed in US3108097), buthiazide (which may be prepared as disclosed in British Patent Nos. 861 ,367), and hydrochlorothiazide), loop diuretics (e.g. bumetanide, ethacrynic acid, furosemide, and torasemide), potassium sparing agents (e.g. amiloride, and triamterene (CAS Number 396-01-O)), and aldosterone antagonists (e.g. spironolactone (CAS Number 52-01-7), epirenone, and the **like); β-adrenergic blockers such as Amiodarone (Cordarone, Pacerone), bunolol hydrochloride** (CAS RN 31969-05-8, Parke-Davis), acebutolol (±N-[3-Acetyl-4-[2-hydroxy-3-[(1 methylethyl)amino]propoxy]phenyl]-butanamide, or (±)-3'-Acetyl-4'-[2-hydroxy -3-

(isopropylamino) propoxy] butyranilide), acebutolol hydrochloride (e.g. Sectral®, Wyeth-Ayerst), alprenolol hydrochloride (CAS RN 13707-88-5 see Netherlands Patent Application No. 6,605,692), atenolol (e.g. Tenormin®, AstraZeneca), carteolol hydrochloride (e.g. Cartrol® Filmtab®, Abbott), Celiprolol hydrochloride (CAS RN 57470-78-7, also see in US4034009), cetamolol hydrochloride (CAS RN 77590-95-5, see also US4059622), labetalol hydrochloride (e.g. Normodyne®, Schering), esmolol hydrochloride (e.g. Brevibloc®, Baxter), levobetaxolol hydrochloride (e.g. Betaxon™ Ophthalmic Suspension, Alcon), levobunolol hydrochloride (e.g. **Betagan® Liquifilm® with C CAP® Compliance Cap, Allergan), nadolol (e.g. Nadolol, Mylan),** practolol (CAS RN 6673-35-4, see also US3408387), propranolol hydrochloride (CAS RN 318-98-9), sotalol hydrochloride (e.g. Betapace AF™,Berlex), timolol (2-Propanol,l-[(l,l-dimethylethyl)amino]-3-[[4-4(4-morpholinyl)-l,2,5-thiadiazol-3-yl]oxy]-, hemihydrate, (S)-, CAS RN 91524-16-2), timolol maleate (S)-I -[(1,1 -dimethylethyl) amino]-3-[[4- (4-morpholinyl)-l,2,5-thiadiazol -3- yl] oxy]-2-propanol (Z)-2-butenedioate (1 :1) salt, CAS RN 26921-17-5), bisoprolol (2-Propanol, l-[4-[[2-(l-methylethoxy)ethoxy]-methyl]phenoxyl]-3-[(l-meth- ylethyl)amino]-, (±), CAS RN 66722-44-9), bisoprolol fumarate (such as (±)-l-[4-[[2-(l-Methylethoxy) ethoxy]methyl]phenoxy]-3-[(l-methylethyl)amino]-2-propanol (E) -2-butenedioate (2:1) (salt), e.g., Zebeta™ , Lederle Consumer), nebivalol (2H-l-Benzopyran-2-**methanol, αα'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also** U.S. Pat. No. 4,654,362), cicloprolol hydrochloride, such 2-Propanol, l-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[l-methylethyl)amino]-, hydrochloride, A.A.S. RN 63686-79-3), dexpropranolol hydrochloride (2-Propanol,l-[l-methylethy)-amino]-3-(l-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9), diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(l-methyl-ethyl)amino]propoxy] [phenyl]-, monohydrochloride CAS RN 69796-04-9), dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[l-hydroxy-2-[l-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride, CAS RN 75659-08-4), exaprolol hydrochloride (2-Propanol, 1 -(2-cyclohexylphenoxy)-3 - [(1 -methylethyl)amino] -, hydrochloride CAS RN 59333-90-3), flestolol sulfate (Benzoic acid, 2-fluro-,3-[[2-[aminocarbonyl)amino]- - dimethylethyl]amino]-2-hydroxypropyl ester, (+)- sulfate (1 :1) (salt), CAS RN 88844-73-9; metalol hydrochloride (Methanesulfonamide, N-[4-[l-hydroxy-2-(methylamino)propyl]phenyl]-, monohydrochloride CAS RN 7701-65-7), metoprolol 2-

Propanol, l-[4-(2- methoxyethyl)phenoxy]-3-[l-methylethyl)amino]-; CAS RN 37350-58-6), metoprolol tartrate (such as 2-Propanol, l-[4-(2-methoxyethyl)phenoxy]-3-[(l-methylethyl)amino]-, e.g., Lopressor®, Novartis), pamatolol sulfate (Carbamic acid, [2-[4-[2-hydroxy-3-[(l- methylethyl)amino]propoxyl]phenyl]-ethyl]-, methyl ester, (±) sulfate (salt) (2:1), CAS RN 59954-01-7), penbutolol sulfate (2-Propanol, l-(2-cyclopentylphenoxy)-3-[l,l-dimethyle- thyl)amino] 1 , (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5), practolol (Acetamide, N-[4-[2- hydroxy-3-[(l-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4;) tiprenolol hydrochloride (Propanol, l-[(l-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (±), CAS RN 39832-43-4), tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl] amino] ethoxyl]-, CAS RN 38103-61-6), bopindolol, indenolol, pindolol, propanolol, tertatolol, and tilisolol, and the like; calcium channel blockers such as besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-l ,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate, e.g., Norvasc®, Pfizer), clentiazem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-cis)-, (Z)-2-butenedioate (1 :1), see also US4567195), isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-l,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, (±)-4(4-benzofurazanyl)- 1 ,4-dihydro-2,6-dimethyl-3 ,5 -pyridinedicarboxylate, see also US4466972); nimodipine (such as is isopropyl (2- methoxyethyl) 1, 4- dihydro -2,6- dimethyl -4- (3-nitrophenyl) -3,5- pyridine - dicarboxylate, e.g. Nimotop®, Bayer), felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-l,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate- , e.g. Plendil® Extended-Release, AstraZeneca LP), nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-l,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(l-methylethyl) ester, also see US3799934), nifedipine (such as 3, 5 -pyridinedicarboxylic acid,l,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, e.g., Procardia XL® Extended Release Tablets, Pfizer), diltiazem hydrochloride (such as l,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis., e.g., Tiazac®, Forest), verapamil hydrochloride (such as benzeneacetronitrile, (alpha)-[[3-[[2-(3,4-dimethoxyphenyl) ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)-(1 -methylethyl) hydrochloride, e.g., Isoptin® SR, Knoll Labs), teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]4-[2-[(lE)-3-(l,l-dimethylethoxy)-3-oxo- l-

propenyl]phenyl]-l,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4), belfosdil (Phosphonic acid, [2-(2-phenoxy ethyl)- 1,3 -propane- diyl]bis-, tetrabutyl ester CAS RN 103486-79-9), fostedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl]methyl]-, diethyl ester CAS RN 75889-62-2), aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, efonidipine, gallopamil, lacidipine, lemildipine, lercanidipine, monatepil maleate (1-Piperazinebutanamide, N-(6, 11 -dihydrodibenzo(b,e)thiepin- 11 -yl)4-(4-fluorophenyl)-, (+)-, (Z)-2-butenedioate (1 :1) (±)-N-(6,l l-Dihydrodibenzo(b,e)thiep- in-l l-yl)-4-(p- fluorophenyl)-l-piperazinebutyramide maleate (1 :1) CAS RN 132046-06-1), nicardipine, nisoldipine, nitrendipine, manidipine, pranidipine, and the like; T-channel calcium antagonists such as mibefradil; angiotensin converting enzyme (ACE) inhibitors such as benazepril, benazepril hydrochloride (such as 3-[[l-(ethoxycarbonyl)-3- phenyl-(1 S)-propyl]amino]-2,3 ,4,5-tetrahydro-2-oxo- 1 H - 1 -(3 S)-benzazepine- 1 -acetic acid monohydrochloride, e.g., Lotrel®, Novartis), captopril (such as l-[(2S)-3-mercapto-2- methylpropionyl]-L-proline, e.g., Captopril, Mylan, CAS RN 62571-86-2 and others disclosed in US4046889), ceranapril (and others disclosed in US4452790), cetapril (alacepril, Dainippon disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986)), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987), indalapril (delapril hydrochloride (2H-1,2,4- Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1- dioxide CAS RN 2259-96-3); disclosed in US4385051), enalapril (and others disclosed in US4374829), enalopril, enaloprilat, fosinopril, ((such as L-proline, 4-cyclohexyl-l-[[[2-methyl- l-(l-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, e.g., Monopril, Bristol-Myers Squibb and others disclosed in US4168267), fosinopril sodium (L- Proline, 4-cyclohexyl-l-[[(R)-[(lS)-2-methyl-l-(l-ox- opropoxy)propox), imidapril, indolapril (Schering, disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983)), lisinopril (Merck), losinopril, moexipril, moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(lS)- 1 -(ethoxycarbonyl)-3-phenylpropyl]amino]- 1 -oxopropyl]- 1 ,- 2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5), quinapril, quinaprilat, ramipril (Hoechsst) disclosed in EP 79022 and Curr. Ther. Res. 40:74 (1986), perindopril erbumine (such as 2S,3aS,7aS- 1 -[(S)-N-[(S)- 1 -Carboxybutyljalanyljhexahydro^-indolinecarboxylic acid, 1 -ethyl ester, compound with tert-butylamine (1 :1), e.g., Aceon®, Solvay), perindopril (Servier, disclosed in Eur. J. clin.

Pharmacol. 31 :519 (1987)), quanipril (disclosed in US4344949), spirapril (Schering, disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5): 173 (1986)), tenocapril, trandolapril, zofenopril (and others disclosed in US4316906), rentiapril (fentiapril, disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983)), pivopril, YS980, teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7), BRL 36,378 (Smith Kline Beecham, see EP80822 and EP60668), MC-838 (Chugai, see CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986), CGS 14824 (Ciba-Geigy, 3-([l-ethoxycarbonyl-3-phenyl-(lS)-propyl]amino)-2,3,4,5-tetrahydro-2-ox- o-l-(3S)-benzazepine-l acetic acid HCl, see U.K. Patent No. 2103614), CGS 16,617 (Ciba- Geigy, 3(S)-[[(lS)-5-amino-l-carboxypentyl]amino]-2,3,4,- 5-tetrahydro-2-oxo-lH-l- benzazepine-1-ethanoic acid, see US4473575), Ru 44570 (Hoechst, see Arzneimittelforschung 34:1254 (1985)), R 31-2201 (Hoffman-LaRoche see FEBS Lett. 165:201 (1984)), CI925 (Pharmacologist 26:243, 266 (1984)), WY-44221 (Wyeth, see J. Med. Chem. 26:394 (1983)), and those disclosed in US2003006922 (paragraph 28), US4337201, US4432971 (phosphonamidates); neutral endopeptidase inhibitors such as omapatrilat (Vanlev®), CGS 30440, cadoxatril and ecadotril, fasidotril (also known as aladotril or alatriopril), sampatrilat, mixanpril, and gemopatrilat, AVE7688, ER4030, and those disclosed in US5362727, US5366973, US5225401, US4722810, US5223516, US4749688, US5552397, US5504080, US5612359, US5525723, EP0599444, EP0481522, EP0599444, EP0595610, EP0534363, EP534396, EP534492, EP0629627; endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; vasodilators such as hydralazine (apresoline), clonidine (clonidine hydrochloride (1H-Imidazol- 2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-, monohydrochloride CAS RN 4205-91-8), catapres, minoxidil (loniten), nicotinyl alcohol (roniacol), diltiazem hydrochloride (such as 1,5- Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4- methoxyphenyl)-, monohydrochloride, (+)-cis, e.g., Tiazac®, Forest), isosorbide dinitrate (such as l,4:3,6-dianhydro-D-glucitol 2,5-dinitrate e.g., Isordil® Titradose®, Wyeth- Ayerst), sosorbide mononitrate (such as l,4:3,6-dianhydro-D-glucito- 1,5-nitrate, an organic nitrate, e.g., Ismo®, Wyeth-Ayerst), nitroglycerin (such as 2,3 propanetriol trinitrate, e.g., Nitrostat® Parke- Davis), verapamil hydrochloride (such as benzeneacetonitrile, (±)-(alpha)[3-[[2-(3,4 dimethoxypheny l)ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)- (1 -methylethyl) hydrochloride, e.g., Covera HS® Extended-Release, Searle), chromonar (which may be prepared as disclosed in

US3282938), clonitate (Annalen 1870 155), droprenilamine (which may be prepared as disclosed in DE2521113), lidoflazine (which may be prepared as disclosed in US3267104); prenylamine (which may be prepared as disclosed in US3152173), propatyl nitrate (which may be prepared as disclosed in French Patent No. 1,103,113), mioflazine hydrochloride (1 -Piperazineacetamide, 3-(aminocarbonyl)4-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6- dichlorophenyl)-, dihydrochloride CAS RN 83898-67-3), mixidine (Benzeneethanamine, 3,4- dimethoxy-N-(l-methyl-2-pyrrolidinylidene)- Pyrrolidine, 2-[(3,4-dimethoxyphenethyl)imino]- 1 -methyl- l-Methyl-2- [(3, 4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), isosorbide mononitrate (D-Glucitol, l,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7), erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel-CAS RN 7297-25-8), clonitrate(l,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1), dipyridamole Ethanol, 2,2',2",2'"-[(4,8-di-l-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis- CAS RN 58-32-2), nicorandil (CAS RN 65141-46-0 3-), pyridinecarboxamide (N-[2-(nitrooxy)ethyl]-Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9), nifedipine3,5-Pyridinedicarboxylic acid, l,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4), perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1 :1) CAS RN 6724-53-4), oxprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9), pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6), **verapamil (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]- methylamino]propyl]-3, 4-dimethoxy-α-(l -methylethyl)- CAS RN 52-53-9) and the like; angiotensin II receptor** antagonists such as, aprosartan, zolasartan, olmesartan, pratosartan, FI6828K, RNH6270, candesartan (1 H-Benzimidazole-7-carboxylic acid, 2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)[l,l'-biphenyl]4-yl]methyl]- CAS RN 139481-59-7), candesartan cilexetil ((+/-)-l-(cyclohexylcarbonyloxy)ethyl-2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl]-lH-benzimidazole carboxylate, CAS RN 145040-37-5, US5703110 and US5196444), eprosartan (3-[l-4-carboxyphenylmethyl)-2-n-butyl-imidazol-5-yl]-(2-thienylmethyl) propenoic acid, US5185351 and US5650650), irbesartan (2-n-butyl-3- [[2'-(lh-tetrazol-5-yl)biphenyl-4-yl]methyl] 1 ,3-

diazazspiro[4,4]non-l-en-4-one, US5270317 and US5352788), losartan (2-N-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole, potassium salt, US5138069, US5153197 and US5128355), tasosartan (5,8-dihydro-2,4-dimethyl-8-[(2'-(lH-tetrazol-5-yl)[l,r-biphenyl]4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(6H)-one, US5149699), telmisartan (4'-[(1 ,4-dimethyl-2'-propyl-(2,6'-bi-lH-benzimidazol)-r-yl)]-[1 , 1 '-biphenyl]-2-carboxylic acid, CAS RN 144701-48-4, US5591762), milfasartan, abitesartan, valsartan (Diovan® (Novartis), (S)-N-valeryl-N-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl)methyl]valine, US5399578), EXP-3137 (2-N-butyl-4-chloro-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole-5-carboxylic acid, US5138069, US5153197 and US5128355), 3-(2'-(tetrazol-5-yl)-l,r-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, 4'[2-ethyl-4-methyl-6-(5,6,7,8-tetrahydroimidazo[l,2-a]pyridin-2-yl]-benzimidazol-l-yl]-methyl]-l,r-biphenyl]-2- carboxylic acid, 2-butyl-6-(l-methoxy-l-methylethyl)-2-[2'-)IH-tetrazol-5-yl)biphenyl-4-ylmethyl] guinazolin-4(3H)-one, 3 - [2 ' -carboxybiphenyl-4-yl)methyl] -2-cyclopropyl-7-methyl- 3H-imidazo[4,5-b]pyridine, 2-butyl-4-chloro-l-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-carboxylic acid, 2-butyl-4-chloro-l-[[2'-(lH-tetrazol-5- yl) [1 , 1 ' -biphenyl] -4-yl]methyl]- 1 H-imidazole-5 -carboxylic acid- 1 -(ethoxycarbonyl-oxy)ethyl ester potassium salt, dipotassium 2-butyl-4-(methylthio)-l-[[2-[[[(propylamino)carbonyl]amino]-sulfonyl](l,l '-biphenyl)-4-yl]methyl]-l H-imidazole-5 -carboxylate, methyl-2-[[4-butyl-2-methyl-6-oxo-5-[[2'-(lH-tetrazol-5-yl)-[l,l '-biphenyl]-4-yl]methyl]-l-(6H)- pyrimidinyl]methyl]-3-thiophencarboxylate, 5-[(3,5-dibutyl-lH-l,2,4-triazol-l-yl)methyl]-2-[2- (1 H-tetrazol-5 -ylphenyl)]pyridine, 6-butyl-2-(2-phenylethyl)-5 [[2'-(I H-tetrazol-5 -yl)[1,1 '- biphenyl]-4-methyl]pyrimidin-4-(3H)-one D,L lysine salt, 5-methyl-7-n-propyl-8-[[2'-(lH- tetrazol-5-yl)biphenyl-4-yl]methyl]-[1 ,2,4]-triazolo[1 ,5-c]pyrimidin-2(3H)-one, 2,7-diethyl-5- [[2'-(5-tetrazoly)biphenyl-4-yl]methyl]-5H-pyrazolo[l,5-b][l,2,4]triazole potassium salt, 2-[2- butyl-4,5-dihydro-4-oxo-3-[2'-(lH-tetrazol-5-yl)-4-biphenylmethyl]-3H-imidazol[4,5- c]pyridine-5-ylmethyl]benzoic acid, ethyl ester, potassium salt, 3-methoxy-2,6-dimethyl-4- [[2'(lH-tetrazol-5-yl)-l,l '-biphenyl-4-yl]methoxy]pyridine, 2-ethoxy-l-[[2'-(5-oxo-2,5-dihydro- 1 ,2,4-oxadiazol-3 -yl)biphenyl-4-yl]methyl] - 1 H-benzimidazole-7-carboxylic acid, 1 - [N-(2 ' -(1 H- tetrazol-5-yl)biphenyl-4-yl-methyl)-N-valerolylaminomethyl)cyclopentane- 1 -carboxylic acid, 7- methyl-2n-propyl-3-[[2' lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo[4,5-6]pyridine, 2- [5-[(2-

ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl]-2-quinolinyl]sodium benzoate, 2-butyl-6-chloro-4-hydroxymethyl-5 -methyl-3 -[[2'-(I H-tetrazol-5 -yl)biphenyl-4-yl]methyl]pyridine, 2- [[[2-butyl- 1 - [(4-carboxyphenyl)methyl] - 1 H-imidazol-5 -yl]methyl]amino]benzoic acid tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-6-one, 4(S)- [4-(carboxymethyl)phenoxy]-N-[2(R)-[4-(2-sulfobenzamido)imidazol- 1 -yl]octanoyl]-L-proline, 1 - (2,6-dimethylphenyl)-4-butyl-l,3-dihydro-3-[[6-[2-(lH-tetrazol-5-yl)phenyl]-3-pyridinyl]methyl]-2H-imidazol-2-one, 5 ,8-ethano-5 ,8-dimethyl-2-n-propyl-5 ,6,7,8-tetrahydro-1 - [[2'(lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-lH,4H-l,3,4a,8a-tetrazacyclopentanaphthalene-9-one, 4-[l-[2'-(l,2,3,4-tetrazol-5-yl)biphen-4-yl)methylamino]-5,6,7,8-tetrahydro-2-trifylquinazoline, 2-(2-chlorobenzoyl)imino-5-ethyl-3-[2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl-l,3,4-thiadiazoline, 2-[5-ethyl-3-[2-(lH-tetrazole-5-yl)biphenyl-4-yl]methyl-l,3,4-thiazoline-2-ylidene]aminocarbonyl-l-cyclopentencarboxylic acid dipotassium salt, and 2-butyl-4-[N-methyl-N-(3 -methylcrotonoyl)amino] - 1 - [[2 ' -(1 H-tetrazol-5 -yl)biphenyl-4-yl]methyl]- 1 H- imidzole-5 -carboxylic acid 1-ethoxycarbonyloxyethyl ester, those disclosed in patent publications EP475206, EP497150, EP539086, EP539713, EP535463, EP535465, EP542059, EP497121, EP535420, EP407342, EP415886, EP424317, EP435827, EP433983, EP475898, EP490820, EP528762, EP324377, EP323841, EP420237, EP500297, EP426021, EP480204, EP429257, EP430709, EP434249, EP446062, EP505954, EP524217, EP514197, EP514198, EP514193, EP514192, EP450566, EP468372, EP485929, EP503162, EP533058, EP467207 EP399731, EP399732, EP412848, EP453210, EP456442, EP470794, EP470795, EP495626, EP495627, EP499414, EP499416, EP499415, EP511791, EP516392, EP520723, EP520724, EP539066, EP438869, EP505893, EP530702, EP400835, EP400974, EP401030, EP407102, EP411766, EP409332, EP412594, EP419048, EP480659, EP481614, EP490587, EP467715, EP479479, EP502725, EP503838, EP505098, EP505111 EP513,979 EP507594, EP510812, EP511767, EP512675, EP512676, EP512870, EP517357, EP537937, EP534706, EP527534, EP540356, EP461040, EP540039, EP465368, EP498723, EP498722, EP498721, EP515265, EP503785, EP501892, EP519831, EP532410, EP498361, EP432737, EP504888, EP508393, EP508445, EP403159, EP403158, EP425211, EP427463, EP437103, EP481448, EP488532, EP501269, EP500409, EP540400, EP005528, EP028834, EP028833, EP411507, EP425921, EP430300, EP434038, EP442473, EP443568, EP445811, EP459136, EP483683,

EP518033, EP520423, EP531876, EP531874, EP392317, EP468470, EP470543, EP502314, EP529253, EP543263, EP540209, EP449699, EP465323, EP521768, EP415594, WO92/14468, WO93/08171, WO93/08169, WO91/00277, WO91/00281, WO91/14367, WO92/00067, WO92/00977, WO92/20342, WO93/04045, WO93/04046, WO91/15206, WO92/14714, WO92/09600, WO92/16552, WO93/05025, WO93/03018, WO91/07404, WO92/02508, WO92/13853, WO91/19697, WO91/11909, WO91/12001, WO91/11999, WO91/15209, WO91/15479, WO92/20687, WO92/20662, WO92/20661, WO93/01177, WO91/14679, WO91/13063, WO92/13564, WO91/17148, WO91/18888, WO91/19715, WO92/02257, WO92/04335, WO92/05161, WO92/07852, WO92/15577, WO93/03033, WO91/16313, WO92/00068, WO92/02510, WO92/09278, WO9210179, WO92/10180, WO92/10186, WO92/10181, WO92/10097, WO92/10183, WO92/10182, WO92/10187, WO92/10184, WO92/10188, WO92/10180, WO92/10185, WO92/20651, WO93/03722, WO93/06828, WO93/03040, WO92/19211, WO92/22533, WO92/06081, WO92/05784, WO93/00341, WO92/04343, WO92/04059, US5104877, US5187168, US5149699, US5185340, US4880804, US5138069, US4916129, US5153197, US5173494, US5137906, US5155126, US5140037, US5137902, US5157026, US5053329, US5132216, US5057522, US5066586, US5089626, US5049565, US5087702, US5124335, US5102880, US5128327, US5151435, US5202322, US5187159, US5198438, US5182288, US5036048, US5140036, US5087634, US5196537, US5153347, US5191086, US5190942, US5177097, US5212177, US5208234, US5208235, US5212195, US5130439, US5045540, US5041152, and US5210204, and pharmaceutically **acceptable salts and esters thereof; α/β adrenergic blockers such as nipradilol, arotinolol,** amosulalol, bretylium tosylate (CAS RN: 61-75-6), dihydroergtamine mesylate (such as **ergotaman-3', 6',18-trione,9,-10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5'(α))-,** monomethanesulfonate, e.g., DHE 45® Injection, Novartis), carvedilol (such as (±)-l-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl] amino] -2-propanol, e.g., Coreg®, SmithKline Beecham), labetalol (such as 5-[l-hydroxy-2-[(l-methyl-3-phenylpropyl) amino] ethyljsalicylamide monohydrochloride, e.g., Normodyne®, Schering), bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-methylbenzenesulfonic acid (1 :1) CAS RN 61-75-6), phentolamine mesylate (Phenol, 3-[[(4,5-dihydro-lH-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1),

solypertine tartrate (5H-l,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-l-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1 :1) CAS RN 5591-43-5), zolertine hydrochloride (Piperazine, l-phenyl4-[2-(lH-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) **CAS RN 7241-94-3) and the like; α adrenergic receptor blockers, such as alfuzosin (CAS RN:** 81403-68-1), terazosin, urapidil, prazosin (Minipress®), tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, XENOlO, fenspiride hydrochloride (which may be prepared as disclosed in US3399192), proroxan (CAS RN 33743-96-3), and labetalol **hydrochloride and combinations thereof; α 2 agonists such as methyldopa, methyldopa HCL,** lofexidine, tiamenidine, moxonidine, rilmenidine, guanobenz, and the like; aldosterone inhibitors, and the like; renin inhibitors including Aliskiren (SPPlOO; Novartis/Speedel); angiopoietin-2-binding agents such as those disclosed in WO03/030833; anti-angina agents such as ranolazine (hydrochloride 1-Piperazineacetamide, N-(2,6- dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635- 56-6), betaxolol hydrochloride (2-Propanol, l-[4-[2 (cyclopropylmethoxy)ethyl]phenoxy]-3-[(l- methylethyl)amino]-, hydrochloride CAS RN 63659-19-8), butoprozine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indolizinyl)-, monohydrochloride CAS RN 62134-34-3), cinepazet maleatel-Piperazineacetic acid, 4-[l-oxo-3-(3,4,5- trimethoxyphenyl)-2-propenyl]-, ethyl ester, (2Z)-2-butenedioate (1 :1) CAS RN 50679-07-7), tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN **32295-184), verapamilhydrochloride (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3 ,4-dimethoxy-α-(1 -methylethyl)-,** monohydrochloride CAS RN 152-114), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), and ranolazine hydrochloride (1 -Piperazineacetamide, N-(2,6-dimethylphenyl)4-[2-hydroxy-3-(2-meth-oxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184); adrenergic stimulants such as guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride, e.g., Tenex® Tablets available from Robins); methyldopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2H -l,2,4-benzothiadiazine-7- sulfonamide

1,1-dioxide, e.g., the combination as, e.g., Aldoril® Tablets available from Merck), methyldopa-chlorothiazide (such as 6-chloro-2H-l, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and methyldopa as described above, e.g., Aldoclor®, Merck), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(l-hydroxy-3-oxo-l-isoindolinyl) benzenesulfonamide), e.g., Combipres®, Boehringer Ingelheim), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, e.g., Catapres®, Boehringer Ingelheim), clonidine (lH-Imidazol-2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-CAS RN 4205-90-7), Hyzaar (Merck; a combination of losartan and hydrochlorothiazide), Co-Diovan (Novartis; a combination of valsartan and hydrochlorothiazide, Lotrel (Novartis; a combination of benazepril and amlodipine) and Caduet (Pfizer; a combination of amlodipine and atorvastatin), and those agents disclosed in US20030069221.

1.3.2.11 Agents for the Treatment of Respiratory Disorders

[172] The GCC agonist peptides described herein can be used in combination therapy with one or more of the following agents useful in the treatment of respiratory and other disorders including but not limited to: (1) β-agonists including but not limited to : albuterol (PRO VENTIL® , S ALBUT AMOl® , VENTOLIN®), bambuterol, bitoterol, clenbuterol, fenoterol, formoterol, isoetharine (BRONKOSOL®, BRONKOMETER®), metaproterenol (ALUPENT®, METAPREL®), pirbuterol (MAXAIR®), reproterol, rimiterol, salmeterol, terbutaline (BRETHAIRE®, BRETHINE®, BRICANYL®), adrenalin, isoproterenol (ISUPREL®), epinephrine bitartrate (PRIMATENE®), ephedrine, orciprenline, fenoterol and isoetharine; (2) steroids, including but not limited to beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, hydrocortisone, methyl prednisone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetonide; (3) β2-agonist-corticosteroid combinations [e.g., salmeterol-fluticasone (AD V AIR®), formoterol-budesonid (S YMBICORT®)] ; (4) leukotriene D4 receptor antagonists/leukotriene antagonists/LTD4 antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafhiukast, montelukast, montelukast sodium (SINGULAIR®), pranlukast, iralukast,

pobilukast, SKB-106,203 and compounds described as having LTD4 antagonizing activity described in U.S. Patent No. 5,565,473; (5) 5 -lipoxygenase inhibitors and/or leukotriene biosynthesis inhibitors [e.g., zileuton and BAY1005 (CA registry 128253-31-6)]; (6) histamine Hl receptor antagonists/antihistamines (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: astemizole, acrivastine, antazoline, azatadine, azelastine, astamizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chloropheniramine maleate, cimetidine clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylarnine, ebastine, efletirizine, epinastine, famotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norasternizole, noraztemizole, phenindamine, pheniramine, picumast, promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; (7) an anticholinergic including but not limited to: atropine, benztropine, biperiden, flutropium, hyoscyamine (e.g. Levsin®; Levbid®; Levsin/SL®, Anaspaz®, Levsinex timecaps®, NuLev®), ilutropium, ipratropium, ipratropium bromide, methscopolamine, oxybutinin, rispenzepine, scopolamine, and tiotropium; (8) an anti-tussive including but not limited to: dextromethorphan, codeine, and hydromorphone; (9) a decongestant including but not limited to: pseudoephedrine and phenylpropanolamine; (10) an expectorant including but not limited to: guafenesin, guaicolsulfate, terpin, ammonium chloride, glycerol guaicolate, and iodinated glycerol; (11) a bronchodilator including but not limited to: theophylline and aminophylline; (12) an anti-inflammatory including but not limited to: fluribiprofen, diclophenac, indomethacin, ketoprofen, S-ketroprophen, tenoxicam; (13) a PDE (phosphodiesterase) inhibitor including but not limited to those disclosed herein; (14) a recombinant humanized monoclonal antibody [e.g. xolair (also called omalizumab), rhuMab, and talizumab]; (15) a humanized lung surfactant including recombinant forms of surfactant proteins SP-B, SP-C or SP-D [e.g. SURFAXIN®, formerly known as dsc-104 (Discovery Laboratories)], (16) agents that inhibit epithelial sodium channels (ENaC) such as amiloride and related compounds; (17) antimicrobial agents used to treat pulmonary infections such as acyclovir,

amikacin, amoxicillin, doxycycline, trimethoprin sulfamethoxazole, amphotericin B, azithromycin, clarithromycin, roxithromycin, clarithromycin, cephalosporins(ceffoxitin, cefmetazole etc), ciprofloxacin, ethambutol, gentimycin, ganciclovir, imipenem, isoniazid, itraconazole, penicillin, ribavirin, rifampin, rifabutin,amantadine, rimantidine, streptomycin, tobramycin, and vancomycin; (18) agents that activate chloride secretion through Ca++ dependent chloride channels (such as purinergic receptor (P2Y(2) agonists); (19) agents that decrease sputum viscosity, such as human recombinant DNase 1, (Pulmozyme®); (20) nonsteroidal anti-inflammatory agents (acemetacin, acetaminophen, acetyl salicylic acid, alclofenac, alminoprofen, apazone, aspirin, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusinal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen, ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, miroprofen, mofebutazone, nabumetone oxaprozin, naproxen, naproxen, niflumic acid , oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxican, sulfasalazine, sulindac, sulindac, suprofen, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, tolmetin, zidometacin, zomepirac, and zomepirac); and (21) aerosolized antioxidant therapeutics such as S-Nitrosoglutathione.

1.3.2.12 Anti-Diabetic Agents

[173] The GCC agonist peptides described herein can be used in therapeutic combination with **one or more anti-diabetic agents, including but not limited to: PPARγ agonists such as glitazones** (e.g., WAY-120,744, AD 5075, balaglitazone, ciglitazone, darglitazone (CP-86325, Pfizer), englitazone (CP-68722, Pfizer), isaglitazone (MIT/J&J), MCC- 555 (Mitsibishi disclosed in US5594016), pioglitazone (such as such as Actos™ pioglitazone; Takeda), rosiglitazone (Avandia™;Smith Kline Beecham), rosiglitazone maleate, troglitazone (Rezulin®, disclosed in US4572912), rivoglitazone (CS-Ol 1, Sankyo), GL-262570 (Glaxo Welcome), BRL49653 (disclosed in WO98/05331), CLX-0921, 5-BTZD, GW-0207, LG- 100641, JJT-501

(JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/Pfizer), NN-2344 (Dr. Reddy/NN), YM-440 (Yamanouchi), LY-300512, LY-519818, R483 (Roche), T131 (Tularik), and the like and compounds disclosed in US4687777, US5002953, US5741803, US5965584, US6150383, US6150384, US6166042, US6166043, US6172090, US6211205, US6271243, US6288095, US6303640, US6329404, US5994554, W097/10813, WO97/27857, WO97/28115, WO97/28137,WO97/27847, WO00/76488, WO03/000685,WO03/027112,WO03/035602, WO03/048130, WO03/055867, and pharmaceutically acceptable salts thereof; biguanides such as metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride, such as Glucophage™, Bristol-Myers Squibb); metformin hydrochloride with glyburide, such as Glucovance™, Bristol-Myers Squibb); buformin (Imidodicarbonimidic diamide, N-butyl-); etoformine (l-Butyl-2-ethylbiguanide, Schering A. G.); other metformin salt forms (including where the salt is chosen from the group of, acetate, benzoate, citrate, ftimarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutarnate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate), and phenformin; protein tyrosine phosphatase- IB (PTP-IB) inhibitors, such as A-401,674, KR 61639, OC- 060062, OC-83839, OC-297962, MC52445, MC52453, ISIS 113715, and those disclosed in WO99/585521, WO99/58518, WO99/58522, WO99/61435, WO03/032916, WO03/032982, WO03/041729, WO03/055883, WO02/26707, WO02/26743, JP2002114768, and pharmaceutically acceptable salts and esters thereof; sulfonylureas such as acetohexamide (e.g. Dymelor, Eli Lilly), carbutamide, chlorpropamide (e.g. Diabinese®, Pfizer), gliamilide (Pfizer), gliclazide (e.g. Diamcron, Servier Canada Inc), glimepiride (e.g. disclosed in US4379785, such as Amaryl , Aventis), glipentide, glipizide (e.g. Glucotrol or Glucotrol XL Extended Release, Pfizer), gliquidone, glisolamide, glyburide/glibenclamide (e.g. Micronase or Glynase Prestab, Pharmacia & Upjohn and Diabeta, Aventis), tolazamide (e.g. Tolinase), and tolbutamide (e.g. Orinase), and pharmaceutically acceptable salts and esters thereof; meglitinides such as repaglinide (e.g. Pranidin®, Novo Nordisk), KAD1229 (PF/Kissei), and nateglinide (e.g. Starlix®, Novartis), and pharmaceutically

acceptable salts and esters thereof; α glucoside hydrolase inhibitors (or glucoside inhibitors) such as acarbose (e.g. Precose™, Bayer disclosed in US4904769), miglitol (such as GLYSET™, Pharmacia & Upjohn disclosed in US4639436), camiglibose (Methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2- (hydroxymethyl)piperidino]-alpha-D-glucopyranoside, Marion Merrell Dow), voglibose (Takeda), adiposine, emiglitate, pradimicin-Q, salbostatin, CKD-711, MDL-25,637, MDL- 73,945, and MOR 14, and the compounds disclosed in US4062950, US4174439, US4254256, US4701559, US4639436, US5192772, US4634765, US5157116, US5504078, US5091418, US5217877, US51091 and WOO 1/47528 (polyamines); α-amylase inhibitors such as tendamistat, trestatin, and Al -3688, and the compounds disclosed in US4451455, US4623714, and US4273765; SGLT2 inhibtors including those disclosed in US6414126 and US6515117; an aP2 inhibitor such as disclosed in US6548529; insulin secreatagogues such as linogliride, A-4166, forskilin, dibutyrl cAMP, isobutylmethylxanthine (IBMX), and pharmaceutically acceptable salts and esters thereof; fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and pharmaceutically acceptable salts and esters thereof; A2 antagonists, such as midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan, and pharmaceutically acceptable salts and esters thereof; insulin and related compounds (e.g. insulin mimetics) such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente), Lys-Pro insulin, GLP-I (1-36) amide, GLP-I (73-7) (insulintropin, disclosed in US5614492), LY-315902 (Lilly), GLP-I (7-36)-NH2), AL-401 (Autoimmune), certain compositions as disclosed in US4579730, US4849405, US4963526, US5642868, US5763396, US5824638, US5843866, US6153632, US6191105, and WO 85/05029, and primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form (sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin), also see the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins); non-thiazolidinediones such as JT-501 and farglitazar (GW-2570/GI- 262579), and pharmaceutically acceptable salts and esters thereof; PPARα/γ dual agonists such as AR-HO39242 (Aztrazeneca), GW-409544 (Glaxo-Wellcome), BVT-142, CLX-0940, GW-1536, GW-1929, GW-2433, KRP-

297 (Kyorin Merck; 5-[(2,4-Dioxo thiazolidinyl)methyl] methoxy-N-[[4-(trifluoromethyl)phenyl] methyljbenzamide), L-796449, LR-90, MK-0767 (Merck/Kyorin/Banyu), SB 219994, muraglitazar (BMS), tesaglitzar (Astrazeneca), reglitazar (JTT-501) and those disclosed in WO99/16758, WO99/19313, WO99/20614, WO99/38850, WO00/23415, WO00/23417, WO00/23445, WO00/50414, WO01/00579, WO01/79150, WO02/062799, WO03/004458, WO03/016265, WO03/018010, WO03/033481, WO03/033450, WO03/033453, WO03/043985, WO 031053976, U.S. application Ser. No. 09/664,598, filed Sep. 18, 2000, Murakami et al. Diabetes 47, 1841-1847 (1998), and pharmaceutically acceptable salts and esters thereof; other insulin sensitizing drugs; VPAC2 receptor agonists; GLK modulators, such as those disclosed in WO03/015774; retinoid modulators such as those disclosed in **WO03/000249; GSK 3β/GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl-lH-**imidazol-5- yl]pyridine and those compounds disclosed in WO03/024447, WO03/037869, WO03/037877, WO03/037891, WO03/068773, EP1295884, EP1295885, and the like; glycogen phosphorylase (HGLPa) inhibitors such as CP-368,296, CP-316,819, BAYR3401, and compounds disclosed in WOO 1/94300, WO02/20530, WO03/037864, and pharmaceutically acceptable salts or esters thereof; ATP consumption promotors such as those disclosed in WO03/007990; TRB3 inhibitors; vanilloid receptor ligands such as those disclosed in WO03/049702; hypoglycemic agents such as those disclosed in WO03/015781 and WO03/040114; glycogen synthase kinase 3 inhibitors such as those disclosed in WO03/035663 agents such as those disclosed in WO99/51225, US20030134890, WO01/24786, and WO03/059870; insulin-responsive DNA binding protein-1 (IRDBP-I) as disclosed in WO03/057827, and the like; adenosine A2 antagonists such as those disclosed in WO03/035639, **WO03/035640, and the like; PPARδ agonists such as GW 501516, GW 590735, and compounds** disclosed in JP10237049 and WO02/14291; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, NVP-DPP728A (1- [[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999), P32/98, NVP-LAF-237, P3298, TSL225 (tryptophyl-l,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), valine pyrrolidide, TMC-2A/2B/2C, CD- 26 inhibitors, FE999011, P9310/K364, VIP 0177, DPP4, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as

disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) ,and the compounds disclosed in US6395767, US6573287, US6395767 (compounds disclosed include BMS-477118, BMS-471211 and BMS 538,305), WO99/38501, WO99/46272, WO99/67279, WO99/67278, WO99/61431WO03/004498, WO03/004496, EP1258476, WO02/083128, WO02/062764, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/000180, and WO03/000181; GLP-I agonists such as exendin-3 and exendin-4 (including the 39 aa polypeptide synthetic exendin-4 called Exenatide®), and compounds disclosed in US2003087821 and NZ 504256, and pharmaceutically acceptable salts and esters thereof; peptides including amlintide and Symlin® (pramlintide acetate); and glycokinase activators such as those disclosed in US2002103199 (fused heteroaromatic compounds) and WO02/48106 (isoindolin-1-one-substituted propionamide compounds).

EXAMPLES

Example 1: Clinical Study for safety and efficacy in humans for the treatment of chronic idiopathic constipation

[174] A randomized, double-blind, placebo-controlled, 14-day repeat oral, dose ranging study was conducted in patients with chronic idiopathic constipation (CIC). The primary objective of this study was to evaluate the safety of SP-304 (1.0 mg, 3.0 mg, 9.0 mg and 0.3 mg) for 14 days in patients with CIC. One secondary objective was to assess the pharmacokinetic profile of SP-304 in plasma. Other secondary objectives included evaluations of pharmacodynamic effects (efficacy) on parameters such as the time to first bowel movement after daily dosing with SP-304, bowel habits over time – for example, spontaneous bowel movements (SBMs), complete spontaneous bowel movements (CSBMs), and stool consistency [using Bristol Stool Form Scale (BSFS)] – and other patient reported outcomes such as abdominal discomfort.

[175] The study included five arms with assigned interventions as indicated in the table below.

Arms	Interventions
SP-304 1.0 mg: Experimental	Subjects receiving SP-304 1.0 mg for 14 consecutive days
SP-304 3.0 mg: Experimental	Subjects receiving SP-304 3.0 mg for 14 consecutive days
SP-304 9.0 mg: Experimental	Subjects receiving SP-304 9.0 mg for 14 consecutive days
Placebo: Placebo Comparator	Subjects receiving Placebo for 14 consecutive days
SP-304 0.3 mg: Experimental	Subjects receiving SP-304 0.3 mg for 14 consecutive days

[176] Subjects diagnosed with CIC were screened for the anticipated 4 cohorts to yield 80 randomized subjects for enrollment. There were four dose cohorts (1.0 mg, 3.0mg, 9.0 mg and 0.3 mg) with 20 subjects per dose cohort [randomization ratio 3:1 (15 receive SP-304:5 receive placebo)]. Subjects who continued to meet all the entry criteria and complete the pre-treatment bowel movement (BM) diary received, in a double-blind, randomized fashion, SP-304 or matching placebo. The entry criteria included (1) meeting modified ROME III criteria for chronic constipation (CC); (2) no significant finding in colonoscopy within past 5 years; (3) good health as determined by physical examination, medical history, vital signs, ECG, clinical chemistry, hematology, urinalysis, drug screen and serology assessments; and (4) during 14-day pre-treatment period, subjects reporting < 6 SBM and < 3 CSBM in each pre-treatment week. All subjects receiving at least one dose of SP-304 or matching placebo were considered evaluable for the safety endpoints (78 total). If a subject did not have a major protocol deviation, had at least 5 days of study treatment each week and corresponding entries for bowel habits, he/she was considered evaluable for efficacy parameters (54-55 total).

[177] The demographics of the subjects in the study are summarized in the table below.

	Placebo	0.3 mg	1.0 mg	3.0 mg	9.0 mg
			Age		
	47.7 (14.6)	51.1 (12.0)	50.5 (10.6)	48.5 (16.1)	47.3 (12.7)
			Gender		
Female	18 (90.0%)	12 (85.7%)	14 (100%)	13 (86.7)	12 (80%)
Male	2 (10.0%)	2 (14.3%)	0	2 (13.3%)	3 (20%)
			Race		
White	17 (85.0%)	13 (92.9%)	12 (85.7%)	14 (93.3%)	12 (80.0%)

African American	1 (5.0%)	0	1 (7.1%)	0	2 (13.3%)
Asian	1 (5.0%)	1 (7.1%)	1 (7.1%)	0	1 (6.7%)
American Indian	1 (5.0%)	0	0	0	0
Other	0	0	0	1 (6.7%)	0

Values for age are the mean (standard deviation); values for gender and race are the number (percentage of experimental arm).

Results

[178] Pharmacokinetics and Safety:

[179] There was no detectable systemic absorption of plecanatide (assay sensitivity $\geq$ 10 ng/mL). No serious adverse events (SAE) were reported in subjects receiving plecanatide and no deaths reported in this study. 10% (2/20) subjects who received placebo and 17.2% (10/58) subjects who received SP-304 reported adverse events considered as related to the treatment. The majority of adverse events were mild / moderate and transient in nature. 10% (2/20) subjects who received placebo and 5.2% (3/58) subjects who received SP-304 reported GI-related adverse events considered as related to treatment. There was no diarrhea reported for any subject receiving SP-304. The table below is a GI-related adverse event (AE) summary.

	Placebo n=20	**0.3 mg n=14**	**1.0 mg n=14**	**3.0 mg n=15**	**9.0 mg n=15**
Abdominal Cramping	1 (5.0%)	0	0	0	0
Abdominal Pain	1 (5.0%)	0	0	0	0
Bloating	0	0	0	0	1 (6.7%)
Diarrhea	1 (5.0%)	0	0	0	0
Flatulence	2 (10.0%)	0	0	0	0
Nausea	0	1 (7.1%)		0	0
Upset Stomach	0	0	0	1 (6.7%)	0

Values are the number (percentage of experimental arm).

[180] Efficacy:

[181] SP-304 (plecanatide) treatment decreased the time to first bowel movement, increased stool frequency (SBM and CSBM), improved stool consistency, and reduced straining and abdominal discomfort. See Figures 1-6.

Example 2: Composition of Wet Granulation batch 10005

Item No.	Ingredient	Use	Concentration % w/w
1	SP304		0.23
2	Mannogem EZ, USP/EP (Mannitol)	Diluent	79.77
3	PROSOLV SMCC 90 LM (silicified microcrystalline cellulose)	Binder	15.0
4	Purified Water (chilled to 5°C), USP	vehicle	n/a
5	Purified Water (chilled to 5°C), USP		n/a
6	Explotab (Sodium Starch Glycolate)	Disintregant	4.0
7	Pruv (sodium stearyl fumarate)	Lubricant	1.0
	Total		100

Example 3: Composition of Wet Granulation batch 10007

Item No.	Ingredient	Use	Concentration % w/w
1	SP304		0.3
3	PROSOLV SMCC 90 HD (silicified microcrystalline cellulose)	Binder	95.7
4	Purified Water (chilled to 5°C), USP	vehicle	n/a
5	Purified Water (chilled to 5°C), USP		n/a

6	Explotab (Sodium Starch Glycolate)	Disintregant	4.0
	Total		100

Example 4: EXCIPIENT COMPATIBILITY

[182] Binary mixtures of SP-304 were prepared and stored in glass vials. For solid excipients the binary mixtures were comprised of 9.1% or 50% excipient. Glass vials were stored at 40C/75RH open or closed. The percent purity (measured by HPLC) of the GCC agonist peptide (SP-304) after storage for the time indicated in each column (i.e., 1, 2, or 3 months for the closed vial and 0.5, 1, 2, or 3 months for the open vials) is indicated by numerical values.

		Closed			Open			
PURPOSE	EXCIPIENT	1M	2M	3M	0.5M	1M	2M	3M
None	None	91.4	88.2	84.1	93.7	91.2	88.2	84.8
Diluent	Sorbitol	92.4	90.1	87.2	92.2	90.8	87.1	80.9
	Mannitol	91.9	88.4	85.1	92.6	90.5	87.9	83.8
	Prosolv	92.2	89.6	86.3	93	90.5	87.8	83.7
	Starch	91.4	88.7	85.4	92.5	90.5	87.9	83.7
Binder	Emdex	91.3	88.7	85.2	91.8	90.7	87.9	81.9
	Plasdone	92.8	90.6	85.6	93.1	90.4	87.3	83
Disintegrant	Explotab	91.9	89.4	87.1	92.2	90.3	84.7	78.3
	Polyplasdone	92	89	85.6	93.5	90.3	87.4	83.1
Glidant	Cabosil	92.1	88.3	85.6	92.6	90.5	87.3	84
Lubricant	Mg stearte	91.5	87.7	84.6	92.6	90.6	87.6	83.8
	PRUV	92	88.3	85.7	92.2	90.5	87.5	83.8
	compritol	90.8	87.1	84.4	92	90.5	86.7	84.1
Excipient	PEG 3350	90.9	87	83.3	91.5	89.4	84.4	77.5
Antioxidant	Ascorbic acid	91.3	86.9	83	92.8	90	85.7	83.8
	BHA	91.9	88.9	85.9	93.5	90.8	87.4	85.8
	BHT	90.8	87.2	84.6	92.4	90.3	86.6	83.6
	EDTA	90.9	87.5	84.1	92.3	90.4	86.7	84.6
Capsule	HPMC capsule	92.2	89	85.2	92.3	90.2	86.4	83.5
	Gelatin capsule	91.5	88.3	84.3	84.3	90.5	86.7	83.6

Liquid for liquid filled capsule	Medium chain trig		90.4					
	PG dicaprylocaprate		89.3					
	Vit E		90					
	Soybean oil		89.6					
	Cremaphor		79.7					
	PG		3.4					
	PG 400		0.7					

Example 5: Geometric dry mix for 0.3mg capsule

[183] Place 12g mannitol in mortar. Add 4g SP-304 and gently mix until a visually uniform powder is obtained. Transfer to Turbula mixer. Rinse mortar with mannitol and transfer to Turbula mixer and mix at high speed for 10 minutes. Add about 150g of mannitol to 4 quart V-shell mixer. Transfer the contents of the Turbula mixer to the V-shell and add 150g of mannitol mix. Discharge v-shell contents and screen through 40 mesh and return to mixer. Add 586g of mannitol to mixer and mix for 20 minutes.

Example 6: Wet granulation process:

[184] Batch 017-10005 comprised of mannitol and low-moisture (2.4%) PROSOLV LM90 (0.33 g/mL) was sprayed with SP-304 solution and fluid bed dried resulted in granulation water content of 0.35%. The final blend contained 1% water, flowed well, and filled capsules well. The 2nd prototype 017-1006 comprised of the same components was adjusted to obtain a target capsule fill weight of 100 mg based on the results of the 1st batch. Water was sprayed onto powder blend with SP-304. The inlet temperature was 50C and the granulation was dried for 1.5 hours and stopped when the product temperature reached 36C. The 3rd (batch017-10006) and 4th (batch 017-10007) capsule prototypes will use PROSOLV HD90, which is a higher density material with superior flow properties and higher moisture content of 5.5% than the PROSOLV LM90. The moisture content of the PROSOLV HD90 is readily removed by fluid bed drying.

The density of PROSOLV HD90 is about 0.55 g/mL. The PRUV lubricant will be removed for these batches.

Example 7: Wet granulation stability

[185] SP-304 was extracted from the capsules by sonication at either at room temperature (RT) or cold temperature and the amount of peptide was determined by HPLC. Initial percentages are based on the amount stated on the label.

Batch	% peptide (initial)	% peptide (1 mos at RT)
017-10006	101.1 (sonicated RT)	97.6 (sonicated cold)
017-10008	97.5 (sonicated RT)	108.2 (sonciated cold)

Example 8: 1M capsule stability in HDPE Bottles

[186] Capsules contained 0.3 mg SP-304 with the remainder of the fill weight (up to 5 mg) made up by mannitol (Perlitol 300 DC). Each capsule contained 1.5% by weight SP-304 and 98.5% mannitol. The capsule shell was composed of HPMC. Amounts are relative to the amount specified on the label (i.e., 0.30 mg peptide). The indicated number of capsules was placed in a high density polyethylene bottle with an induction seal and molecular sieve desiccant for 1 month at either 2-8C (first two columns) or 25C and 60% relative humidity (last two columns). The initial amount of peptide present was 101% of the label claim. The last row gives the amount of peptide remaining after 1 month storage at the indicated temperature as determined by HPLC.

2-8C	2-8C	25C/60RH	25C/60RH
1-capsule per bottle	6-capsules per bottle	1-capsule per bottle	6-capsules per bottle
100%	92%	92%	98%

Example 9: Composition of batch 1528-2855-RD (capsules) and spray coating and drying process

Item No.	Ingredient	Amount per unit (mg)	Concentration % w/w
1	SP-304	0.3246	0.3246
2	Microcrystalline cellulose (Celphere SCP-100)	99.10	99.10
3	Calcium chloride dihydrate	0.2622	0.2622
4	Leucine USP	0.1171	0.1171
5	Hypromellose (Methocel E5 PremLV)	0.2000	0.2000
6	Purified Water, USP	7.2 mL*	n/a
	Total	100	100

*: The amount of water is calculated based on use of 119.0 mL purified water for the whole batch containing 5.356 g SP-304.

[187] The spray drying process of making the batch 2855-RD is described below.

Preparation of Coating Dispersion:

[188] Purified water was added to a glass container and stirred such that a liquid vortex was produced without introducing air. Then calcium chloride dihydrate was slowly added into the water. The mixture was stirred until the salt was dissolved or well dispersed. Next, leucine was slowly added and the resulting mixture was stirred until the amino acid was dissolved or well dispersed. Afterward, methocel was slowly added and the mixture was stirred until methocel was completely dissolved. The solution could be warmed up to dissolve methocel, if necessary. The resulting excipient solution was allowed to cool to room temperature and pass through 80 mesh screen. Then, 127.9g of screened excipient solution was added to a glass container and placed in an ice bath for 0.5 to 1 hour until the solution reached 0 °C. Next, SP-304 was added into the cold excipient solution. The mixture was stir vigorously to allow the peptide to dissolve

in the cold solution. The resulting peptide solution was kept cold in the ice bath as a spraying/coating solution.

Drug Layering

[189] A Glatt GPCG-2 fluid bed processor (with top spray tower) with a Wurster insert was set up for drug layering onto Celphere SCP-100 beads. After loading the Wurster column with Celphere SCP-100 beads, bed temperature was raised to 35 °C and maintained for 30 minutes with minimum fluidization of the beads. The bed temperature was reduced until an exhaust temperature of 35 °C was achieved. The pump tubing of the peristaltic pump used was primed by circulating the spraying solution mentioned above. After the spraying apparatus was adjusted to obtain a satisfactory spray pattern, the coating solution was sprayed onto Celphere SCP-100 beads until all coating solution was sprayed. Operating parameters were recorded. The bed temperature and fluidization were maintained until the beads were sufficiently dry. The fluidization was then reduced while the bed temperature was maintained at 35 °C for 10 minutes. 2g of beads were sampled for moisture analysis when the bed temperature was kept at 35 °C. When the moisture of the sampled beads reached < 5% moisture, the coated beads were discharged and loaded into a dry container. LOD (loss on drying) 2.399%.

Example 10: Composition of batch 1528-2851-RD (tablets) and spray coating and drying process

Item No.	Ingredient	Amount per unit (mg)	Concentration % w/w
1	SP-304	0.3246	0.3607
2	Microcrystalline cellulose (Avicel PH 102)	88.88	98.75
3	Calcium chloride dihydrate	0.2622	0.2913
4	Leucine USP	0.1171	0.1301
5	Hypromellose (Methocel E5 PremLV)	0.2000	0.2222

6	Magnesium stearate	0.225	0.2500
7	Purified Water, USP	7.2 mL*	n/a
	Total	90.0	100

*: The amount of water is calculated based on use of 119.0 mL purified water for the whole batch containing 5.356 g SP-304.

[190] The spray coating and drying process of making the batch 2851-RD is described below.

Preparation of Coating Dispersion:

[191] Purified water was added to a glass container and stirred such that a liquid vortex was produced without introducing air. Then calcium chloride dihydrate was slowly added into the water. The mixture was stirred until the salt was dissolved or well dispersed. Next, leucine was slowly added and the resulting mixture was stirred until the amino acid was dissolved or well dispersed. Afterward, methocel was slowly added and the mixture was stirred until methocel was completely dissolved. The solution could be warmed up to dissolve methocel, if necessary. The resulting excipient solution was allowed to cool to room temperature and pass through 80 mesh screen. Then, 127.9g of screened excipient solution was added to a glass container and placed in an ice bath for 0.5 to 1 hour until the solution reached 0 °C. Next, SP-304 was added into the cold excipient solution. The mixture was stir vigorously to allow the peptide to dissolve in the cold solution. The resulting peptide solution was kept cold in the ice bath as a spraying/coating solution.

Drug Layering

[192] A Glatt GPCG-2 fluid bed processor (with top spray tower) with a Wurster insert was set up for drug layering onto Avicel PH 102 beads. After loading the Wurster column with Avicel PH 102 beads, temperature was raised to 35 °C and maintained for 30 minutes with minimum fluidization of the beads. The bed temperature was reduced until an exhaust temperature of 35 °C was achieved. The pump tubing of the peristaltic pump used was primed by circulating the spraying solution mentioned above. After the spraying apparatus was adjusted to obtain a satisfactory spray pattern, the coating solution was sprayed onto Avicel PH 102 beads until all coating solution was sprayed. Operating parameters were recorded. The bed temperature and

fluidization were maintained until the beads were sufficiently dry. The fluidization was then reduced while the bed temperature was maintained at 35 °C for 10 minutes. 2g of beads were sampled for moisture analysis when the bed temperature was kept at 35 °C. When the moisture of the sampled beads reached < 5% moisture, the coated beads were discharged and loaded into a dry container. LOD (loss on drying) <5%.

[193] The net weight of the coated blend was determined for calculation of the amount of magnesium stearate needed to lubricate the blend. Then the magnesium stearate was added to the coated blend and the mixture was blended for 1 minute.

Compression

[194] A Fette tablet press was set up. Then the blend mixture was loaded into the powder hopper and tooling was installed. The weight of each tablet was set to be 90 mg±5% and hardness to be 4-6 Kp. The weight, hardness and thickness of tablets were measured and recorded every 5 to 10 minutes. Friability measurement was also performed to ensure satisfactory product.

Example 11: Composition of batch 1528-2850-RD (capsules) and process

Item No.	Ingredient	Concentration % w/w
1	SP-304	0.3246
2	Microcrystalline cellulose (Avicel PH 102)	99.43
3	Magnesium stearate	0.2500
4	HPMC capsule shells	n/a
	Total	100

[195] The dry blend process of making the batch 2850-RD is described below.

Blending:

[196] Avicel PH 102 was screened through a 60 mesh screen. V-blenders (1 Qt, 4Qt, and 16 Qt) were then dusted by the screened Avicel PH 102. SP-304 was screened through a 200 mesh screen and loaded into the 1-Qt V-blender. Then, about 80 g Avicel PH 102 was added into the 1-Qt blender and the mixture was blended for 10 minutes at 25 rpm. The mixture was then transferred to the 4-Qt V-blender which was pre-dusted by the screened Avicel PH 102. The 1-Qt blender was rinsed with Avicel and the rinse material was transferred to the 4-Qt blender. The rinsing was repeated until all SP-304 was transferred to the 4-Qt blender. About 200g Avicel was added to the 4-Qt V-blender and the mixture was blended for 10 minutes. The resulting blend was then screened through a 60 mesh screen and then transferred into the pre-dusted 16-Qt blender (dusted with 1500g Avicel). The 4-Qt blender was rinsed with Avicel and the rinse material was transferred to the 16-Qt blender. The remaining Avicel was added to the 16-Qt blender and the mixture was blended for 10 minutes. The resulting blend was passed through Comil and then returned to the 16-Qt blender and was further blended for 5 minutes. Proper amount of magnesium stearate was weighed, screened through a 60 mesh screen, and added into the 16-Qt blender. The resulting mixture was blended for 2 minutes.

Encapsulation

[197] A MG2 Planeta capsule filler was set up. Average weight of the empty capsule shells was determined and target capsule fill weight was calculated (±5%). The blend from the above process was added into the hopper of the capsule filler and encapsulation was started. Run weight parameters were manually adjusted. Resulting capsules were then sorted according to the target fill weight.

Example 12: Composition of batch 1528-2850B-RD (tablets) and process

Item No.	Ingredient	Concentration % w/w
1	SP-304	0.3246
2	Microcrystalline cellulose (Avicel PH	99.43

	102)	
3	Magnesium stearate	0.2500
	Total	100

[198] The dry blend process of making the batch 2850B-RD is described below.

Blending:

[199] Avicel PH 102 was screened through a 60 mesh screen. V-blenders (1 Qt, 4Qt, and 16 Qt) were then dusted by the screened Avicel PH 102. SP-304 was screened through a 200 mesh screen and loaded into the 1-Qt V-blender. Then, about 80 g Avicel PH 102 was added into the 1-Qt blender and the mixture was blended for 10 minutes at 25 rpm. The mixture was then transferred to the 4-Qt V-blender which was pre-dusted by the screened Avicel PH 102. The 1-Qt blender was rinsed with Avicel and the rinse material was transferred to the 4-Qt blender. The rinsing was repeated until all SP-304 was transferred to the 4-Qt blender. About 200g Avicel was added to 4-Qt V-blender and the mixture was blended for 10 minutes. The resulting blend was then screened through a 60 mesh screen and then transferred into the pre-dusted 16-Qt blender (dusted with 1500g Avicel). The 4-Qt blender was rinsed with Avicel and the rinse material was transferred to the 16-Qt blender. The remaining Avicel was added to the 16-Qt blender and the mixture was blended for 10 minutes. The resulting blend was passed through Comil and then returned to the 16-Qt blender and was further blended for 5 minutes. Proper amount of magnesium stearate was weighed, screened through a 60 mesh screen, and added into the 16-Qt blender. The resulting mixture was blended for 2 minutes.

Compression

[200] A Fette tablet press was set up. Then the blend mixture was loaded into the powder hopper and tooling was installed. The weight of each tablet was set to be 90 mg±5% and hardness to be 4-6 Kp. The weight, hardness, and thickness of tablets were measured and recorded every 5 to 10 minutes. Friability measurement was also performed to ensure satisfactory product.

Example 13: Composition of dry blend tablet formulation 1528-3161-RD, 1mg for vacuum drying

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Microcrystalline cellulose (Avicel PH 102)	98.57
3	Magnesium stearate	0.2500
	Total	100

Example 14: Composition of dry blend tablet formulation 1528-3162-RD, 1mg with low-moisture cellulose

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Microcrystalline cellulose (Avicel PH 112)	97.09
3	Magnesium stearate	0.2500
	Total	100

Example 15: Composition of spray coated trehalose granules tablet formulation 1528-3170-RD, 1mg

Item No.	Ingredient	Concentration % w/w

1	SP-304	1.176
2	Trehalose granules	70.48
3	Methocel ES Premium LV	0.50
4	Histidine (in coating solution)	0.9225
5	Calcium ascorbate	0.100
6	Purified water	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Histidine	0.5535
10	Magnesium stearate	0.2500
	Total	100

The process for making spray coated trehalose Granules tablet formulation 1528-3170-RD is described below.

Preparation of the Coating Dispersion

[201] Add purified water to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until **methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50** ºC). Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Add Calcium Ascorbate to solution. Stir until materials are

dissolved. Adjust pH to 7.0 with 1N NaOH solution if pH >7.0. Record adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.107 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Add Histidine to solution. Stir not more than 10min to dissolve the material. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution. Coating Solution must be used within 30min to avoid coloration.

Drug Layering

[202] Setup Glatt GPCG2 with Wurster insert according to SOP EQP-OCM-064 for drug layering onto Trehalose Granules with coating dispersion. Use Glatt GPCG2 In-process form, "EQP-OCM-064-F1," to record in-process information. Turn unit on and preheat column. Fluid Bed Processor: Glatt GPCG-2. Filter: 200 micron screen. Product Container: 4" wurster, stainless steel. Insert height from bottom: 1". Spray direction: Top Spray. Fluid Nozzle Size/ Type: 1mm. Pump: Peristaltic, Master Flex LS. Tubing: Nalge #14 Silicon. Bed **Temperature: ≤ 40°C. Inlet air temperature: Adjust to meet bed temperature target. Outlet air** temperature: Monitor & record. Spray rate: initial rate 4-6g/min, adjust as required. Atomizing air pressure: 20 psi. Air flow: 60cmh and adjust for fluidization. Prepare double polyethylene bags large enough to hold drug layered Granules. Load column with Trehalose. Increase bed temperature to 35°C and maintain for 30 minutes with minimum fluidization of the Granules. Reduce bed temperature until an exhaust temperature of 35 °C is achieved. Prime pump tubing by circulating spraying solution; must not use more than 40g for tubing priming. Adjust the spraying apparatus to obtain satisfactory spray pattern. Coating Solution Weight after priming should > 317g. Record initial weight below before spraying onto trehalose. Start spraying the coating solution onto Trehalose Granules. Record operating parameters on fluid bed processing form. Stop spraying when 297.2 g of coating solution has been sprayed. Maintain bed temperature and continue fluidization until Granules are sufficiently dry. Reduce fluidization

and maintain bed temperature at 35°C for 10 minutes. Do not cool down the Granules. Sample 2g for moisture analysis until moisture is below 1%. Discharge coated Granules into pre-prepared and labeled container (with tare weight) lined with double polyethylene bag. Calculate net weight of drug layered Granules. Setup Lyophilizer per SOP EQP-OCM-00002. Load drug layered granules into a Lyoguard tray (Save bags). Use recipe 3 to dry blend overnight. Discharge dried blend into saved polyethylene bags. Obtain final moisture of the dried granules. Record final Moisture (<1%). Calculate net weight of dried Granules.

Blending

[203] Screen required Avicel and pass through 60 mesh screen. Setup 4 qt V-blender per SOP EQP-OCM-00056. Weigh amount of Histidine needed and blend with small amount of Avicel weighed. Charge into 4 qt. V-blender. Transfer Plecanatide Dried Granules into the V-Blender. Rinse 2-3 times the Lyoguard tray from Step 24 with adequate amount of Weighed Avicel .Transfer rinses into 4 qt. V-b;ender. Transfer all remaining Pre-weighed/screened Avicel into the V-Blender. Mix for 15 minutes. Weigh and screen Magnesium Stearate through a 60 mesh screen. Charge Magnesium Stearate to the 4 qt V-Blender. Ensure the cover is securely closed with no potential powder leakage during blending. Blend for 2 minutes.

Compression

[204] Set-up Korsch press per SOP EQP-OCM-00087. Install 0.250" Standard Concave Round Plain tolling. Obtain blend Assay results and calculate Target Tablet Weight. Acceptable weight range of tablets is ± 5.0%. Load the Final Blend into the powder hopper. Refill as necessary. Adjust fill weight to obtain tablets in the range of 95.0 - 105.0mg and hardness in the range of 4-6kP. Verify friability is NMT 1.0%. Check 5 tablet weights periodically every 5-10min to ensure tablet weight is within the range and record on form QRA-DOC-00011-F6. After tablet weights are recorded, obtain and record 3 tablet hardness and thickness during the periodic weight check. Continue to compress acceptable tablets until the blend is used up. Once press is running properly to achieve specifications above, perform final Friability test and record results (Spec: NMT 1.0%).

Example 16: Composition of spray coated trehalose granules tablet formulation 1528-3171-RD, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.167
2	Trehalose granules	70.31
3	Methocel ES Premium LV	0.50
4	Arginine	1.657
5	Calcium ascorbate	0.100
6	Water for injection	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Magnesium stearate	0.2500
	Total	100

[205] The process for making spray coated trehalose Granules tablet formulation 1528-3171-RD is described below.

Preparation of Coating Solution

Add purified water (Item 6) to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until **methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50** °C). Record appearance of solution. Solution must be cooled before adding other materials.

Add Trehalose to solution. Stir until materials are dissolved. Record appearance of solution. Add Arginine to solution. Stir until materials are dissolved. Record appearance of solution. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Record appearance of solution. Adjust solution pH to pH 8.5 - 8.6 with concentrated HCl followed by adjust pH to 8.3 – 8.4 with 10N HCl. Record final adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.006 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Weigh 5.0g of WFI to rinse API container. Carefully rinse the side of coating solution container and completely transfer the rinse back to the coating solution container. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution (~360.3 g). Coating Solution must be used within as soon as possible.

Drug Layering

[206] Setup Glatt GPCG2 with Wurster insert according to SOP EQP-OCM-064 for drug layering onto Trehalose Granules with coating dispersion. Use Glatt GPCG2 In-process form, "EQP-OCM-064-F1," to record in-process information. Turn unit on and preheat column.

Fluid Bed Processor: Glatt GPCG-2. Filter: 200 micron screen. Product Container: 4" wurster, stainless steel. Insert height from bottom: 1". Spray direction: Top Spray. Fluid Nozzle Size/ Type: 1mm. Pump: Peristaltic, Master Flex LS. Tubing: Nalge #14 Silicon. Bed **Temperature: ≤ 40°C. Inlet air temperature: Adjust to meet bed temperature target. Outlet air** temperature: Monitor & record. Spray rate: initial rate 4-6g/min, adjust as required. Atomizing air pressure: 20psi. Air flow: 60cmh and adjust for fluidization. Load column with Trehalose G. Increase bed temperature to 35°C and maintain for 30 minutes with minimum fluidization of the Granules. Reduce bed temperature until an exhaust temperature of 35 °C is achieved. Prime pump tubing with coating solution. Must not use more than 40g for tubing priming. Adjust the spraying apparatus to obtain satisfactory spray pattern. Record initial weight below before

spraying onto trehalose. Start spraying the coating solution onto Trehalose Granules. Record operating parameters on fluid bed processing form. Stop spraying when 300.3 g of coating solution has been sprayed. Maintain bed temperature and continue fluidization until Granules are sufficiently dry. Reduce fluidization and maintain bed temperature at 35°C for 10 minutes. Do not cool down the Granules. Sample 2g for moisture analysis until moisture is below 1%. Discharge coated Granules into pre-prepared and labeled container (with tare weight) lined with double polyethylene bag. Calculate net weight of drug layered Granules. If moisture is > 1%, vacuum dry blend as follows: Setup Lyophilizer per SOP EQP-OCM-00002. Load drug layered granules into a Lyoguard tray. Use recipe 3 to dry blend overnight. Discharge dried blend into saved polyethylene bags. Obtain final moisture of the dried granules. Calculate net weight of dried Granules.

Blending

[207] Screen required Avicel and pass through 60 mesh screen. Setup 4 qt V-blender. Transfer Plecanatide Dried Granules into the V-Blender. Save bag for discharging final blend. Rinse 2-3 times the Lyoguard tray and bag with adequate amount of Weighed Avicel. Transfer rinses into 4 qt. V-b;ender. Transfer all remaining Pre-weighed/screened Avicel into the V-Blender. Mix for 20 minutes. Weigh and screen Magnesium Stearate through a 60 mesh screen. Charge Magnesium Stearate to the 4 qt V-Blender. Ensure the cover is securely closed with no potential powder leakage during blending. Blend for 2 minutes. Sample 3 x 350 mg of blend at three locations. Obtain exact weight of each sample that has been transferred into the sampling bottle.

Compression

Set-up Korsch press per SOP EQP-OCM-00087. Install 0.250" Standard Concave Round Plain tolling. Obtain blend Assay results and calculate Target Tablet Weight. Acceptable weight range of tablets is ± 5.0%. Load the Final Blend into the powder hopper. Refill as necessary. Adjust fill weight to obtain tablets in the range of 95.0 - 105.0mg and hardness in the range of 4-6kP. Verify friability is NMT 1.0%. Check 5 tablet weights periodically every 5-10min to ensure tablet weight is within the range. After tablet weights are recorded, obtain and record 3 tablet hardness and thickness during the periodic weight check. Continue to compress acceptable

tablets until the blend is used up. Once press is running properly to achieve specifications above, perform final Friability test and record results (Spec: NMT 1.0%).

Example 17: Composition of spray coated trehalose granules tablet formulation 1528-3172, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.167
2	Trehalose granules	70.81
3	Methocel ES Premium LV	0.50
4	TRIS	1.1524
5	Calcium ascorbate	0.100
6	Water for injection	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Magnesium stearate	0.2500
	Total	100

[208] The process for making spray coated trehalose granules tablet formulation 1528-3172-RD is described below.

Preparation of Coating Solution

[209] Add purified water to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until

methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50°C). Record appearance of solution.

[210] Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Record appearance of solution. Add TRIS to solution. Stir until materials are dissolved. Record appearance of solution. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Record appearance of solution. Obtain solution pH: Adjust pH to pH 7.8 – 7.9 with concentrated HCl followed by adjust pH to 7.7 – 7.6 with 10N HCl. Record final adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.006 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Weigh 5.0g of WFI to rinse API container. Carefully rinse the side of coating solution container and completely transfer the rinse back to the coating solution container. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution (~354.2 g). Coating Solution must be used as soon as possible.

The blending and compression processes for batch 1528-3172-RD are similar to that described above for batch 1528-3171-RD.

Example 18: Composition of 1mg dry blend tablet formulation 1528-2925-RD

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.106
2	Microcrystalline cellulose (Avicel PH 102)	98.64

3	Magnesium stearate	0.2500
	Total	100

Example 19: Composition of 3mg dry blend tablet formulation 1528-2926-RD

Item No.	Ingredient	Concentration % w/w
1	SP-304	3.318
2	Microcrystalline cellulose (Avicel PH 102)	96.43
3	Magnesium stearate	0.2500
	Total	100

[211] Other batches were prepared by the processes similar to those described in Examples 9-12. Their compositions are listed below.

[212] Batch 500-55: 0.33% plecanatide, 95.17% microcyrstalline cellulose, 4.0% sodium starch glycolate, and 0.5% magnesium stearate.

[213] Batches 1528-2907-RD and 2010F100A: 3.318% plecanatide, 96.43% Avicel, and 0.25% Mg stearate.

[214] Batches 1528-2906-RD and 2010F099A: 1.106% plecanatide, 98.65% Avicel, and 0.25% Mg stearate.

[215] Batches 1528-2890-RD and 2010F101A: 0.3246% plecanatide, 99.43% Avicel, and 0.25% Mg stearate.

[216] Formula compositions for batches 11H141, 11H152, and 11H140 in this table below (not previously disclosed) are the same as the formula compositions for GMP stability batches 2010F101A, 2010F099A, and 2010F100A, respectively.

Example 20: Plecanatide tablet and capsule stability

[217] Capsules and tablets of different batches were tested for their stability and the results were provided. Unless otherwise specified, 1M, 2M, 3M, or 4M in the tables below denotes that the measurements were carried out at the end of 1, 2, 3, or 4 month(s) of the storage period.

Potency Summary: This test was performed by taking a composite sample of about 5 units to determine the average potency of the sample. The table below shows the stability of capsules or tablets in terms of potency (% of label claim).

Lot (description)	Bulk*	Package	Potency (% Label Claim)																	
			Storage Condition																	
		Package	Initial	40C/75RH			30C/65RH			25C/60RH				5C						
				1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD (0.3mg dry blend capsules)	88	HDPE bottle		89		87			89			91		80				89.3		89
		Oxyguard bottle		91		91			92			91		79				88.9		90
		Blister strip	90	90		85			88			91		79						90
1528-2855-RD (0.3mg coated bead capsule)	94	HDPE bottle		101		100			96			102		88						98
		Oxyguard bottle		101		96			99			104		87						100
		Blister strip		97		103			99			98		87						97
500-55 (0.3mg dry blend capsule)	97	HDPE bottle		97		94			95			96		84						98
		Oxyguard bottle		98		96			96			102		83						97
		Blister strip	93	97		93			95			106		83						96
1528-2850B-RD (0.3mg dry blend tablet)	76	HDPE bottle		85		88			94			83		67						70
		Oxyguard bottle		84		84			88			74		74						80
1528-2851-RD (0.3mg coated particle tablet)	96	HDPE bottle		115		72			90			99		99						78
		Oxyguard bottle		81		88			83			111		85						96
2010F100A (3mg dry blend capsule)	101	Blister strip	97	95	94	91	95	95	92	97	95	93			97	94	94			
2010F101A (0.3mg dry blend capsule)	97	Blister strip	92	91	91	86	94	92	85	95	93	88			95	95	92			
2010F099A (1mg dry blend capsule)	98	Blister srtip	94	92	91	89	93	94	89	94	94	91			95	94	92			
11H141 (0.3mg dry	103	Blister strip	101	95	92	87	98	93	92	96	92	95			100	97	97			

blend capsule)																				
11H152 (1mg dry blend capsule)	102	Blister strip	97	91	91	93	94	95	96	96	95	96			97	95	97			
11H140 (3mg dry blend capsule)	105	Blister strip	99	94	95	94	95	94	97	99	95	97			99	97	97			
1528-2925-RD (1mg dry blend tablet)	99	Oxyguard 40cc with PharnaKeep											99						103	
1528-2926-RD (3mg dry blend tablet)	100	Oxyguard 40cc with PharnaKeep											94						93	
1528-2907-RD (3mg dry blend capsule)	98																			
1528-2906-RD (1mg dry blend capsule)	98																			
1528-2890-RD (0.3mg dry blend capsule)	93																			

*Blend

[218] As demonstrated by the table above, there was little or no appreciable loss in potency after storage under accelerated conditions (40C/75RH or 30C/65RH), which suggests that these capsules or tablets could be stable at room temperature for 18 months or for longer times if refrigerated or stored at 25C.

[219] Water content summary: The table below shows that the water content was stable over the testing period in the packages evaluated for various capsule/tablet compositions. This further demonstrated that products were stable.

[220]

Lot	Water (in-process)	Packaging	Water packaged product																
			Initial	40C/75RH			30C/65RH			25C/60RH				5C					
				1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD 0.3mg dry blend capsule		32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		5.03		5.64			3.00			2.22		2.39				5.48		1.8
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		5.07		5.24			4.28			5.33		4.08				5.31		3.7
		Blister, N2	4.21	4.87		5.80			4.76			4.31		4.09						2.8
1528-2855-RD 0.3mg coated bead capsule	2.40	32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		0.57		0.47			1.63			0.68		0.42						0.2
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		2.10		1.05			1.29			2.07		0.30						0.8
		Blister strip		0.73		2.11			0.54			0.58		0.32						0.3
500-55 0.3mg dry blend capsule		HDPE bottle		5.63		4.19			5.51			5.79		2.98						2.7
		Oxyguard bottle		5.78		4.69			5.90			5.66		2.99						2.8
		Blister strip	4.09	5.78		4.17			5.53			6.16		3.12						2.9
1528-2850B-RD 0.3mg dry blend tablet		32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		4.09		4.03			6.28			6.10		2.86						2.1
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		4.81		4.91			6.15			6.30		4.05						3.4
1528-2851-RD 0.3mg coated particle tablet	3.32	32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		4.33		4.50			5.09			5.90		2.55						1.5
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		5.15		4.88			5.82			6.02		4.34						3.0
2010F100A (3mg dry blend capsule)		Blister strip	4.7	4.5	4.6	4.4	4.5	4.7	4.4	4.5	4.8	4.4			4.5	4.8	4.5			
2010F101A (0.3mg dry blend capsule)		Blister strip	4.5	4.8	4.7	4.7	4.5	4.7	4.3	4.4	4.7	4.3			4.5	4.7	4.2			
2010F099A (1mg dry blend capsule)		Blister strip	4.6	4.4	4.6	4.4	4.5	4.5	4.3	4.4	4.6	4.4			4.2	4.7	4.3			

11H141 (0.3mg dry blend capsule)		Blister strip	5	4.8	4.9	4.9	5.1	4.9	4.8	5.0	5.0	4.9			5.0	4.9	4.9		
11H152 (1mg dry blend capsule)		Blister strip	5.2	4.8	4.9	4.8	4.8	4.8	4.9	4.8	4.8	4.9			5.0	4.9	4.8		
11H140 (3mg dry blend capsule)		Blister strip	5.2	5.0	5.0	5.0	4.9	5.0	5.0	4.9	5.0	4.9			4.9	4.9	4.8		
1528-2925-RD (1mg dry blend tablet)		Oxyguard 40cc with PharmaKeep											4.9					4.0	
1528-2926-RD (3mg dry blend capsule)		Oxyguard 40cc with PharmaKeep											4.0					4.0	
1528-2907-RD 3mg dry blend capsule		Bulk capsule	4.78																
1528-2906-RD 1m dry blend capsule		Bulk capsule	4.84																
1528-2890-RD		Bulk capsule	4.8																

[221]

Impurity summary: The table below shows the product stability in terms of HPLC or UPLC of total impurities as a function of time and storage condition. The data in the table suggest that the increase in total impurities in tested batches except batch 500-55 be no greater than 7% at room temperature after 18 months. It also suggest that the increase in total impurities in all tested 1528-2855-RD batche in different packages be no greater than 7% at 30 °C for 18 months. It was also observed that the 1528-2855-RD batch had less impurity increase than the 1528- 2850-RD batch or was more stable than the 1528-2850-RD batch.

Batch	Package	Total impurities % area																	
		Initial	40C/75RH			30C/65RH			25C/60RH					5C					
			1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD	HDPE bottle	3.2	5.1		5.9			4.4			3.8		4.8				3.1		3.7
	Oxyguard bottle		5.7		7.4			5.3			4.3		5.3				3.1		3.5
	Blister strip		5.5		7.0			5.0			4.3		5.5						3.7
1528-2855-RD	HDPE bottle	3.5	3.6		5.1			3.8			3.4		4.4						3.4
	Oxyguard bottle		3.9		4.4			4.1			3.7		4.0						3.7
	Blister strip		4.0		5.2			4.0			3.6		4.2						3.8
500-55	HDPE bottle	3.2	5.7		8.4			5.4			4.4		6.0						3.5
	Oxyguard bottle		5.6		7.0			5.1			4.3		5.6						3.5
	Blister strip		6.5		8.0			5.7			4.8		6.5						3.6
1528-2850B-RD	HDPE bottle	3.6	5.0		6.5			4.5			3.9		4.7						3.7
	Oxyguard bottle		5.6		7.3			4.7			4.1		4.9						3.6
1528-2851-RD	HDPE bottle	3.7	4.2		5.1			4.0			3.8		3.9						3.7
	Oxyguard bottle		4.9		6.8			4.7			4.4		4.3						3.9
2010F101A (0.3mg dry blend capsule)	Blister strip	2.1	4.4	3.9	4.7	2.9	3.2	3.4	3.1	2.7	3.2			2.0	1.3	2.0			
2010F099A (1mg dry blend capsule)	Blister strip	2.9	3.7	3.8	4.3	3.1	3.1	3.6	2.7	2.9	3.2			2.4	2.4	2.4			
2010F100A (3mg dry blend	Blister strip	2.4	3.2	3.6	4.2	2.8	2.8	3.0	2.6	2.7	2.9			2.4	2.5	2.7			

capsule)																					
11H141 (0.3mg dry blend capsule)	Blister strip	1.3	3.3	4.2	4.5	2.5	3.6	3.3	2.0	2.8	2.9			1.4	1.5	1.8					
11H152 (1mg dry blend capsule)	Blister strip	2.4	3.6	4.2	4.1	2.6	3.2	3.1	2.6	3.1	2.9			2.3	2.3	2.1					
11H140 (3mg dry blend capsule)	Blister strip	2.1	3.5	3.7	4.5	2.6	2.7	3.3	2.5	2.7	2.9			2.3	2.2	1.8					
1528-2925-RD (1mg dry blend tablet)	Oxyguard 40cc with PharmaKeep											2.7					1.7				
1528-2926-RD (3mg dry blend capsule)	Oxyguard 40cc with PharmaKeep											2.6									
1528-2906-RD	HDPE bottle	1.83		5.18																	
1528-2907-RD	HDPE bottle	1.85		4.58																	
1528-2890-RD	Bulk	1.9																			

Content uniformity: This test was performed by placing 10 individual capsule/tablet units in 10 individual bottles and potency of each unit was measured to show whether individual capsules or tablets have uniform potency (% label claim or %LC).

0.3mg Dry blend tablet 1528-2850B-RD	
	%LC
Sample	**1528-2850B-RD (dry tabs)**
1	78.62
2	91.43
3	86.52
4	90.9
5	84.83
6	95.29
7	75.69
8	76.87
9	84.92
10	86.9
Mean	**85.2**
std. dev	6.51
% RSD	**7.64**

5

0.3mg Coated particle tablet 1528-2851-RD		
Sample	**Weight (mg)**	**% Label Claim**
1	88.86	69.55
2	89	94.41
3	88.89	94.34
4	88.6	72.18
5	88.37	142.52

6	88.76	149.44
7	89.42	78.8
8	88.56	131.08
9	89.08	102.55
10	88.78	99.13
Mean		103.4
St. Dev		28.53
%RSD		27.59

0.3mg Dry blend capsule 1528-2890			3mg Dry blend capsule 1528-2907-RD			1mg Dry blend capsule 1528-2906-RD	
Sample	%LC		Sample	%LC		Sample	%LC
1	87.2		1	94.5		1	98.1
2	94.6		2	101.2		2	101.8
3	92.6		3	97.9		3	93.1
4	94.2		4	94.5		4	97.5
5	93.5		5	95.9		5	97.9
6	91.7		6	95.2		6	97.1
7	91.6		7	96.1		7	94.5
8	99		8	99		8	100.1
9	91.8		9	93.8		9	98.1
10	92.1		10	93.4		10	97.9
Mean	92.8		Mean	96.2		Mean	97.6
RSD	3.20%		RSD	2.60%		RSD	2.50%
AV(10)***	12.8		AV(10)	8.4		AV(10)	6.8

***AV = acceptance value used for UPS <905> content uniformity. Idealy AV should be less than 15 to pass USP <905> content uniformity.

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0.3mg dry blend capsule 1528-2850-RD		
Sample	Original %LC	Re -preparation %LC
1	82.73	85.87
2	84.57	89.45
3	80.29	91.39
4	84.88	88.45
5	85.2	86.96
6	82.9	84.84
7	84.75	86.21
8	86.58	91.37
9	84.34	88.79
10	88.82	84.75
Mean	84.51	87.81
std. dev	2.288445	2.467121
% RSD	2.7	2.8

Conte1528-2855-RD Sample	**%LC**		**1528-2850B-RD Sample**	**%LC**
1	88.82		1	78.62
2	93.73		2	91.43
3	89.06		3	86.52
4	84.94		4	90.9
5	89.93		5	84.83
6	88.7		6	95.29
7	88.71		7	75.69
8	86.85		8	76.87
9	86.92		9	84.92
10	91.33		10	86.9
Mean	**88.9**		**Mean**	**85.2**
std. dev	2.45		std. dev	6.51
% RSD	**2.76**		**% RSD**	**7.64**

500-55	
Sample	% label claim
1	96.90%
2	99.40%
3	103.20%
4	96.90%
5	100.00%
6	99.60%
7	96.90%
8	102.80%
9	96.80%
10	93.90%
Mean	98.60%
SD	2.91
RSD	3.00%
AV	7.1 (PASS)

[222] The data in the tables above show that all of the batches yield very good content uniformity acceptable for commercial product.

[223] Dissolution 50-rpm summary: The tables below are summaries of the dissolution of drug from capsules or tablets in an unconventional small-volume apparatus needed to measure the small amount of drug in the units using slow stirring to look for changes in dissolution over time. The test was performed by placing one unit into a very small volume of water at 37C with a paddle stirring at 50-rpm (which is slow) and data were collected at 15, 30 45, and 60 minutes to show the drug release rate over time. These tested products are "immediate release" oral solid dosage forms and a conventional requirement is to have about 75% released in about 45 minutes. The tables summarize the results at 45 minutes and indicate that dissolution was stable over time.

	Dissolution (% label claim at 45 minutes)							
		Initial		40C/75RH	30C/65RH		25C	5C
Lot (description)		bulk	0M	1M	2M	3M	3M	4M
1528-2850-RD (dry blend V-Cap capsule HDPE bottle)	Vessel 1	85		78	84	81	86	83
	Vessel 2	87		73	90	82	84	85
	Vessel 3	88		79	85	79	91	87
	Vessel 4	84		86	87	78	83	85
	Vessel 5	89		72	89	80	79	90
	Vessel 6	88		81	85	82	88	83
	Average	87		78	87	80	85	85
	RSD	2		6.4	2.7	2.1	5.0	2.9
1528-2850-RD (dry blend Vcap capsule OxyGuard bottle)	Vessel 1	85		69	89	79	88	82
	Vessel 2	87		75	89	87	81	85
	Vessel 3	88		77	87	86	84	86
	Vessel 4	84		80	87	83	83	80
	Vessel 5	89		71	88	89	84	84
	Vessel 6	88		76	88	79	86	89
	Average	87		75	88	84	84	84
	RSD	2		5.3	1.2	5.2	3.1	3.6
1528-2850-RD (dry blend V-cap capsule blister strip)	Vessel 1	85	75	59	86	73	83	
	Vessel 2	87	89	77	79	81	81	
	Vessel 3	88	88	83	87	74	84	
	Vessel 4	84	89	67	93	85	83	
	Vessel 5	89	93	75	82	82	84	
	Vessel 6	88	90	82	90	67	87	
	Average	87	87	74	86	77	84	
	RSD	2	7	12.5	6.3	8.6	2.4	

	Dissolution (% label claim at 45 minutes)					
		Initial	40C/75RH	30C/65RH		25C
Lot (description)		bulk	1M	2M	3M	3M
1528-2855-RD (coated bead V-Cap capsule HDPE bottle)	Vessel 1	104	85	100	79	83
	Vessel 2	89	90	97	83	88
	Vessel 3	91	84	71	91	50

	Vessel 4	88	64	73	94	88
	Vessel 5	94	75	72	75	92
	Vessel 6	93	80	39	96	94
	Average	93	**80**	**75**	**86**	**83**
	RSD	6	**12**	**29**	9.7	20
1528-2855RD (coated bead V-cap capsule OxyGuard bottle)	Vessel 1	104	88	80	87	78
	Vessel 2	89	79	91	86	94
	Vessel 3	91	84	63	92	74
	Vessel 4	88	92	98	90	98
	Vessel 5	94	89	81	81	93
	Vessel 6	93	44	99	81	78
	Average	93	**79**	**85**	**86**	**86**
	RSD	6	**23**	**16**	5.3	12.1
1528-2855-RD (coated bead V-cap capsule blister strip)	Vessel 1	104	85	98	100	81
	Vessel 2	89	84	94	63	80
	Vessel 3	91	97	96	82	87
	Vessel 4	88	94	96	55	74
	Vessel 5	94	64	75	95	66
	Vessel 6	93	96	102	89	82
	Average	93	**87**	**93**	**81**	**78**
	RSD	6	**14**	**10**	22.4	9.2

	Dissolution (% label claim at 45 minutes)				
		Initial	40C/75RH	30C/65RH	
Lot (description)		bulk	1M	2M	3M

1528-2851-RD (coated particle tablet HDPE bottle)	Vessel 1	58%	67	68	89
	Vessel 2	77%	84	78	124
	Vessel 3	57%	62	68	70
	Vessel 4	96%	110	84	105
	Vessel 5	95%	65	107	61
	Vessel 6	64%	103	76	51
	Average	74%	**82**	**80**	**83**
	RSD	24%	**26**	**18**	33
1528-2851-RD (coated particle tablet OxyGuard bottle)	Vessel 1	58%	89	54	118
	Vessel 2	77%	73	101	69
	Vessel 3	57%	75	82	80
	Vessel 4	96%	68	67	73
	Vessel 5	95%	76	162	96
	Vessel 6	64%	97	82	95
	Average	74%	**80**	**91**	**89**
	RSD	24%	**14**	42	**21**

	Dissolution (% label claim at 45 minutes)				
		Initial	40C/75RH	30C/65RH	
Lot (description)		bulk	1M	2M	3M
1528-2850B-RD (dry blend tablet HDPE bottle)	Vessel 1	90%	88	96	92
	Vessel 2	69%	79	82	92
	Vessel 3	83%	76	100	85
	Vessel 4	94%	96	86	94
	Vessel 5	88%	89	89	83
	Vessel 6	92%	83	97	83
	Average	86%	**85**	**92**	**88**
	RSD	11%	**8.2**	**8**	**5.6**
1528-2850B-RD (dry blend tablet OxyGuard bottle)	Vessel 1	90%	74	80	91
	Vessel 2	69%	97	87	95
	Vessel 3	83%	91	86	90
	Vessel 4	94%	94	91	90
	Vessel 5	88%	83	91	89
	Vessel 6	92%	91	76	84
	Average	86%	**88**	**85**	**90**

	RSD	11%	**9.6**	7	**4.0**

	Dissolution (% label claim at 45 minutes)						
		Initial		40C/75RH	30C/65RH		25C
Lot (description)		bulk	0M	1M	2M	3M	3M
500-55 (dry blend V-Cap Plus capsule HDPE bottle)	Vessel 1	95		90	92	91	89
	Vessel 2	98		85	98	97	98
	Vessel 3	69		85	96	94	76
	Vessel 4	94		89	95	100	97
	Vessel 5	99		89	97	98	86
	Vessel 6	104		100	99	94	92
	Average	93		**89**	**96**	**96**	**90**
	RSD	13.1		**6.2**	**2.4**	**3.6**	**9.1**
500-55 (dry blend V-Cap Plus capsule OxyGuard bottle)	Vessel 1	95		84	103	99	94
	Vessel 2	98		97	101	95	103
	Vessel 3	69		97	99	98	97
	Vessel 4	94		92	97	92	96
	Vessel 5	99		91	100	95	101
	Vessel 6	104		96	95	93	91
	Average	93		**93**	**99**	**95**	**97**
	RSD	13.1		**5.3**	**2.7**	**2.7**	**4.3**
500-55 (dry blend V-Cap Plus capsule foil blister)	Vessel 1	95	98	99		89	98
	Vessel 2	98	101	88		94	87
	Vessel 3	69	107	90		89	96
	Vessel 4	94	96	90		86	87
	Vessel 5	99	99	68		89	94
	Vessel 6	104	99	90		82	89
	Average	93	**100**	**87**		**88**	**92**
	RSD	13.1	**3.8**	**11.8**		**4.3**	**5.5**

Dry blend 3mg lot 1528-2907-RD 500-mL				
	15 min	30 min	45 min	60 min
Vessel 1	91	96	97	96
Vessel 2	96	95	97	96

Vessel 3	96	97	97	97
Vessel 4	95	102	100	100
Vessel 5	97	96	96	97
Vessel 6	92	99	98	98
Average	94	97	98	97
RSD	2.7	2.5	1.1	1.4

Dry blend 1mg lot 1528-2906-RD 150-mL				
	15 min	30 min	45 min	60 min
Vessel 1	65	92	96	99
Vessel 2	49	91	95	96
Vessel 3	46	88	96	97
Vessel 4	44	96	101	102
Vessel 5	39	78	93	99
Vessel 6	57	90	95	96
Average	50	89	96	98
RSD	18.8	7	2.8	2.4

Dry blend 0.3mg lot 1528-2890-RD 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	57	94	100	105
Vessel 2	60	96	100	105
Vessel 3	86	93	94	95
Vessel 4	76	90	91	101
Vessel 5	69	90	97	106
Vessel 6	68	95	97	97
Average	69	93	97	102
RSD	15.6	2.8	3.4	4.5

	Capsule Dissolution at 45 minutes												
		5C			25C			30C			40C		
Lot (strength)	COA	1M	2M	3M	1M	2M	3M	1M	2M	3M	1M	2M	3M
2011F101 A (0.3mg)	98%	99%	95%	95%	95%	92%	95%	94%	93%	97%	93%	90%	92%
2011F099 A (1mg)	96%	95%	95%	95%	91%	93%	94%	93%	90%	95%	95%	92%	93%
2011F100 A (3mg)	99%	101%	97%	97%	100 %	95%	95%	98%	95%	95%	96%	93%	95%
11H141 (0.3mg)	101%	102%	101 %	101 %	105 %	96%	106 %	102 %	97%	103 %	99%	96%	98%

11H152 (1mg)	96%	96%	99%	97%	96%	99%	97%	96%	96%	98%	96%	96%	98%
11H140 (3mg)	102%	102%	102 %	101 %	105 %	100%	97%	102 %	99%	102 %	101 %	99%	96%

[224] Dissolution 75-rpm: The tables below show a few examples where the stirring rate was increased slightly to 75-rpm to give more consistent results and indicates stable dissolution after accelerated storage of 1 or 2 months at 40C 75% relative humidity.

Dry blend 0.3mg lot 1528-2850-RD 1M 40C/75RH 75-rpm 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	75	80	80	81
Vessel 2	61	75	80	82
Vessel 3	65	81	83	84
Vessel 4	78	86	84	85
Vessel 5	66	79	83	84
Vessel 6	62	79	84	86
Average	68	80	82	84
RSD	10.3	4.5	2.3	2.2

Dry blend 1mg lot 1528-2906A-RD 2M 40C/75RH 75-rpm 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	69	84	88	88
Vessel 2	62	82	84	85
Vessel 3	65	82	85	85
Vessel 4	58	70	80	79
Vessel 5	59	77	82	81
Vessel 6	68	80	83	84
Average	64	79	84	84
RSD	7.2	6.4	3.3	3.8

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[225] 2855-RD dissolution: The tables below are all the dissolution profiles of batch 1528-2850-RD and indicate stable drug release over time.

	Initial Percent Dissolved

Vessel	15	30	45	60
1	84%	99%	104%	104%
2	28%	80%	89%	92%
3	68%	83%	91%	95%
4	56%	79%	88%	98%
5	29%	83%	94%	98%
6	74%	85%	93%	96%
Mean	57%	85%	93%	97%
RSD	41.20%	8.50%	6.00%	4.20%

1M 40C/75RH OxyGuard Packaging				
Vessel	15 min	30 min	45 min	60 min
1	35	74	88	93
2	46	74	79	85
3	39	78	84	88
4	59	82	92	94
5	22	82	89	92
6	4	20	44	61
Average	**34**	**68**	**79**	**86**
RSD	**57**	**35**	**23**	**14**

2M 30C/65RH OxyGuard				
15 min	30 min	45 min	60 min	
47	67	80	90	
57	80	91	95	
43	55	63	71	
753	92	98	101	
38	64	81	92	
54	94	99	101	
52	**75**	**85**	**92**	
25	**21**	**16**	**12**	

3M 30C/65RH OxyGuard				
15 min	30 min	45 min	60 min	
76	83	87	88	
65	79	86	91	
64	84	92	97	
71	85	90	94	
60	75	81	87	
55	74	81	87	
65	**80**	**86**	**91**	
11.7	5.7	5.3	4.6	

3M 25C/60RH OxyGuard				
15 min	30 min	45 min	60 min	
44	62	78	85	
70	89	94	97	
48	62	74	79	
65	92	98	103	
72	86	93	96	
53	74	78	84	
59	**78**	**86**	**91**	
20.1	17.4	12.1	10.4	

1M 40C/75RH HDPE Bottle				
Vessel	15 min	30 min	45 min	60 min
1	61	78	85	89
2	63	83	90	92
3	66	79	84	91
4	25	44	64	77
5	47	67	75	80
6	57	71	80	85
Average	**53**	**70**	**80**	**86**
RSD	**28**	**20**	**12**	**7**

2M 30C/65RH HDPE				
15 min	30 min	45 min	60 min	
78	97	100	103	
77	93	97	98	
41	59	71	78	
50	65	73	78	
37	59	72	83	
6	21	39	52	
48	**66**	**75**	**82**	
56	**42**	**29**	**22**	

3M 30C/65RH HDPE				
15 min	30 min	45 min	60 min	
58	72	79	85	
51	72	83	90	
53	84	91	94	
66	89	94	95	
48	66	75	81	
85	94	96	99	
60	**80**	**86**	**91**	
22.6	14	9.7	7.3	

3M 25C/60RH HDPE				
15 min	30 min	45 min	60 min	
54	70	83	92	
66	81	88	92	
10	29	50	66	
69	81	88	92	
68	83	92	97	
82	91	94	97	
58	**73**	**83**	**89**	
43	30.6	19.6	13.3	

1M 40C/75RH Blister Packaging				
Vessel	15 min	30 min	45 min	60 min
1	36	69	85	90
2	41	69	84	88

2M 30C/65RH Blister				
15 min	30 min	45 min	60 min	
61	91	98	100	
57	82	94	100	

3M 30C/65RH Blister				
15 min	30 min	45 min	60 min	
82	95	100	102	
31	48	63	74	

3M 25C/60RH Blister				
15 min	30 min	45 min	60 min	
53	71	81	90	
27	57	80	87	

3	67	96	97	98		63	87	96	100		69	77	82	85				
4	54	83	94	104		36	80	96	100		29	41	55	69	70	78	87	92
5	10	46	64	79		45	61	75	83		84	94	95	97	52	66	74	87
6	70	91	96	100		87	100	102	104		74	84	89	82	25	48	66	80
Average	**47**	**76**	**87**	**93**		**58**	**83**	**93**	**98**		**62**	**73**	**81**	**85**	50	74	82	84
RSD	**48**	**25**	**14**	**10**		**30**	**16**	**10**	**8**		40.5	32.1	22.4	14.9	**46**	**66**	**78**	**87**
															37.0	17.0	9.2	5.3

[226] Bathes 2850-RD, 2850B-RD, 2851-RD, and 500-55 were also tested in the similar fashion and all showed stable drug release over time.

We claim:

1. An oral dosage formulation comprising at least one GCC agonist peptide and one or more pharmaceutically acceptable excipients, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 9 and 8.

2. An oral dosage formulation comprising at least one GCC agonist peptide and one or more pharmaceutically acceptable excipients, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249, and the GCC agonist peptide has a chromatographic purity of no less than 91%.

3. The oral dosage formulation of claim 2, wherein the GCC agonist peptide has a chromatographic purity of no less than 92% or no less than 95%.

4. The oral dosage formulation of claim 2, wherein the GCC agonist peptide has a total impurity content of no greater than 9%, 7%, 6%, or 5%,

5. The oral dosage formulation of claim 2, wherein the formulation is substantially free of inorganic acids and carboxylic acids.

6. The oral dosage formulation of claim 2, wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56.

7. The oral dosage formulation of claim 2, wherein the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg or 9.5 mg.

8. The oral dosage formulation of claim 2, wherein the formulation is a solid formulation and the unit dose is a powder, granule, sachet, troche, tablet, or capsule.

9. The oral dosage formulation of claim 2, wherein the one or more pharmaceutically acceptable excipients comprise an inert carrier.

10. The oral dosage formulation of claim 9, wherein the inert carrier is a selected from mannitol, lactose, a microcrystalline cellulose, or starch.

11. The oral dosage formulation of claim 10, wherein the inert carrier has a particle size of from 50 to 900 microns.

12. The oral dosage formulation of claim 2, wherein the one or more pharmaceutically acceptable excipients comprise a divalent cation salt.

13. The oral dosage formulation of claim 12, wherein the salt is calcium chloride or calcium ascorbate.

14. The oral dosage formulation of claim 2, wherein the one or more pharmaceutically acceptable excipients comprise an amino acid or amine, and the molar ratio between the amino acid and GCC agonist peptide is 2:1 to 30:1.

15. The oral dosage formulation of claim 14, wherein the amino acid is leucine, histidine, or arginine.

16. The oral dosage formulation of claim 2, wherein the formulation consists of the GCC agonist peptide, an inert carrier, and a lubricant.

17. The oral dosage formulation of claim 2, wherein the formulation consists of the GCC agonist peptide, an inert carrier, a divalent cation salt, an amino acid, a coating agent and optionally a lubricant.

18. The oral dosage of formulation of claim 17, wherein the inert carrier is microcrystalline cellulose and the lubricant is magnesium stearate.

19. The oral dosage of formulation of claim 18, wherein the divalent cation salt is calcium chloride or calcium ascorbate, the amino acid is leucine, histidine, or arginine, and the coating agent is hypromellose.

20. The oral dosage formulation of claim 2, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

21. The oral dosage formulation of claim 2, wherein the formulation is in the form of a capsule or tablet.

22. The oral dosage formulation of claim 21, wherein the capsule or tablet is in a blister pack or strip.

23. The oral dosage formulation of claim 22, wherein the GCC agonist peptide is in solution or suspension in a lipophilic liquid.

24. The oral dosage formulation of claim 23, wherein the unit dosage form is a liquid-filled capsule.

25. The oral dosage formulation of claim 2, wherein the liquid is a refined specialty oil or a medium chain triglyceride or related ester.

26. A process for making an oral dosage formulation comprising at least one GCC agonist peptide, the method comprising:

a) providing an aqueous solution comprising: a GCC agonist peptide selected from the group consisting of SEQ ID NOs: 1-54 and 56-249, and one or more pharmaceutically acceptable excipients, wherein the concentration of the GCC agonist peptide ranges from 10 to 60 mg/mL; and

b) applying the aqueous solution to a pharmaceutically acceptable carrier to generate a GCC agonist peptide-coated carrier.

27. The process of claim 26, wherein the one or more pharmaceutically acceptable excipients comprise a divalent cation salt wherein the divalent cation is selected from Ca^{2+}, Mg^{2+}, Zn^{2+}, and Mn^{2+}

28. The process of claim 26, wherein the one or more pharmaceutically acceptable excipients comprise an amino acid selected from leucine, histidine, and arginine.

29. The process of claim 26, wherein the one or more pharmaceutically acceptable excipients comprise a coating agent.

30. The process of claim 29, wherein the coating agent is hypromellose.

31. The process of claim 26, wherein the aqueous solution has a pH greater than 4 or 5.

32. The process of claim 26, wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, and 56.

33. The process of claim 26, wherein the aqueous solution is substantially free of inorganic acids and carboxylic acids.

34. The process of claim 26, further comprising drying the GCC agonist peptide-coated carrier.

35. An oral dosage formulation made by the process of claim 26, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

36. A method for treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject an oral dosage formulation of claim 2.

37. The method of claim 36, wherein the disease or disorder is a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, chronic idiopathic constipation, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, constipation, gastroparesis, heartburn, gastric cancer, and H. pylori infection.

38. The method of claim 36, wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56.

39. The method of claim 36, further comprising administering to the subject an effective amount of an inhibitor of a cGMP-specific phosphodiesterase.

40. The method of claim 36, further comprising administering to the subject an effective amount of at least one laxative.

41. The method of claim 36, further comprising administering to the subject an effective amount of at least one anti-inflammatory agent.

42. A pharmaceutical composition comprising the oral dosage formulation of claim 2.

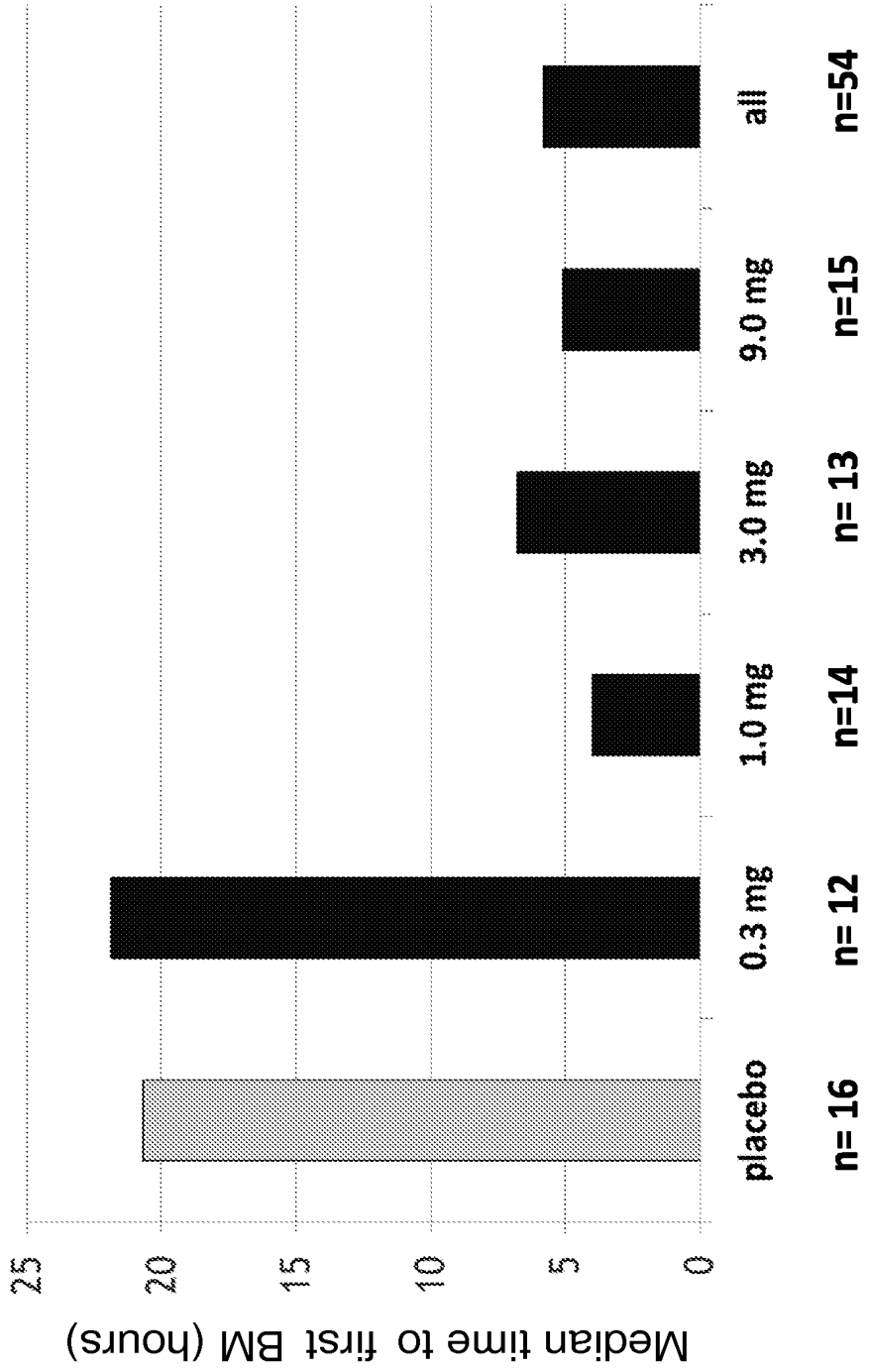
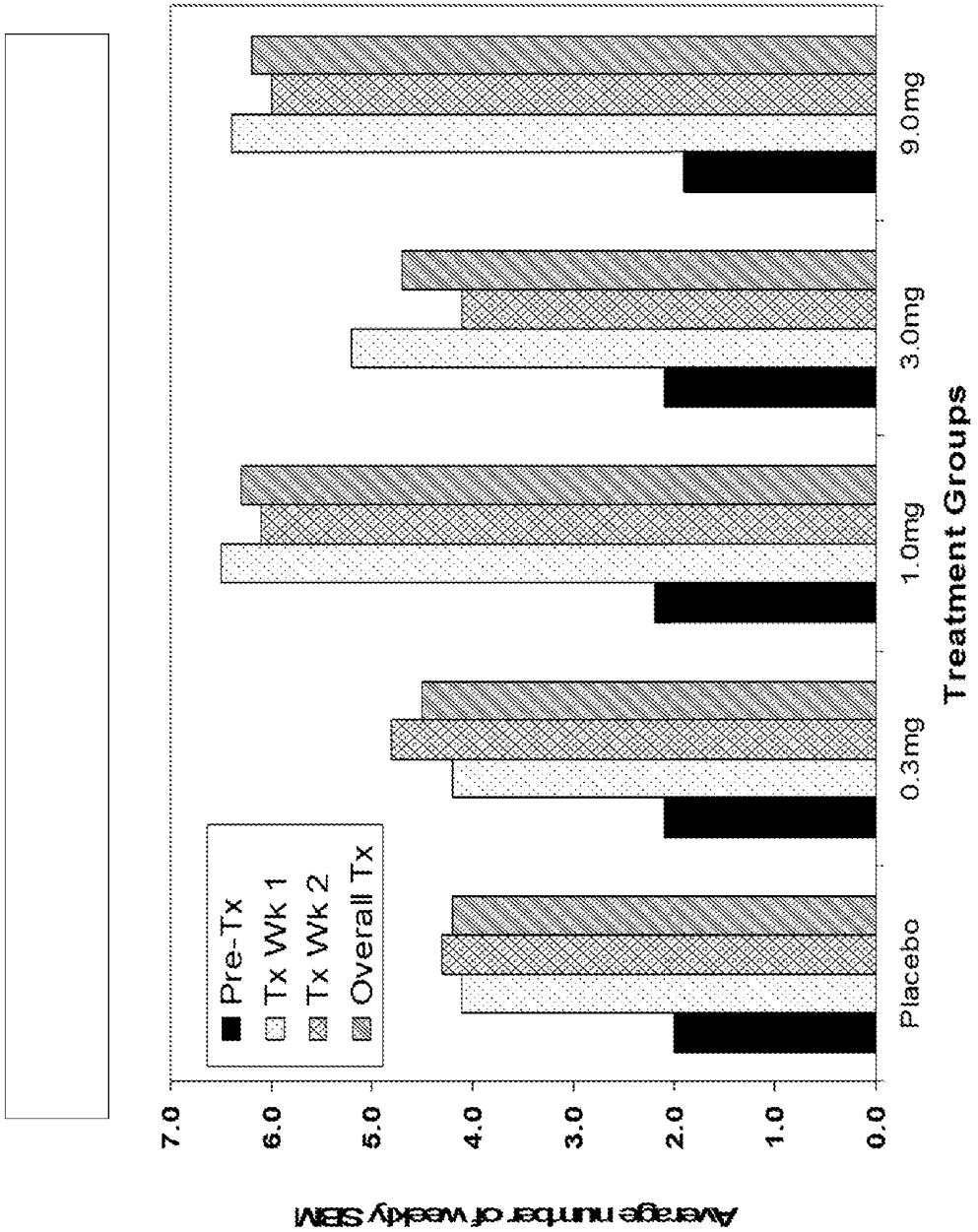

Median time to first BM (hours)
0
5
10
15
20
25
placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
all
n= 16
n= 12
n=14
n= 13
n=15
n=54

Fig. 1


Average number of weekly SEM
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6.0
5.0
4.0
3.0
2.0
1.0
0.0
Pre-Tx
Tx Wk 1
Tx Wk 2
Overall Tx
Placebo
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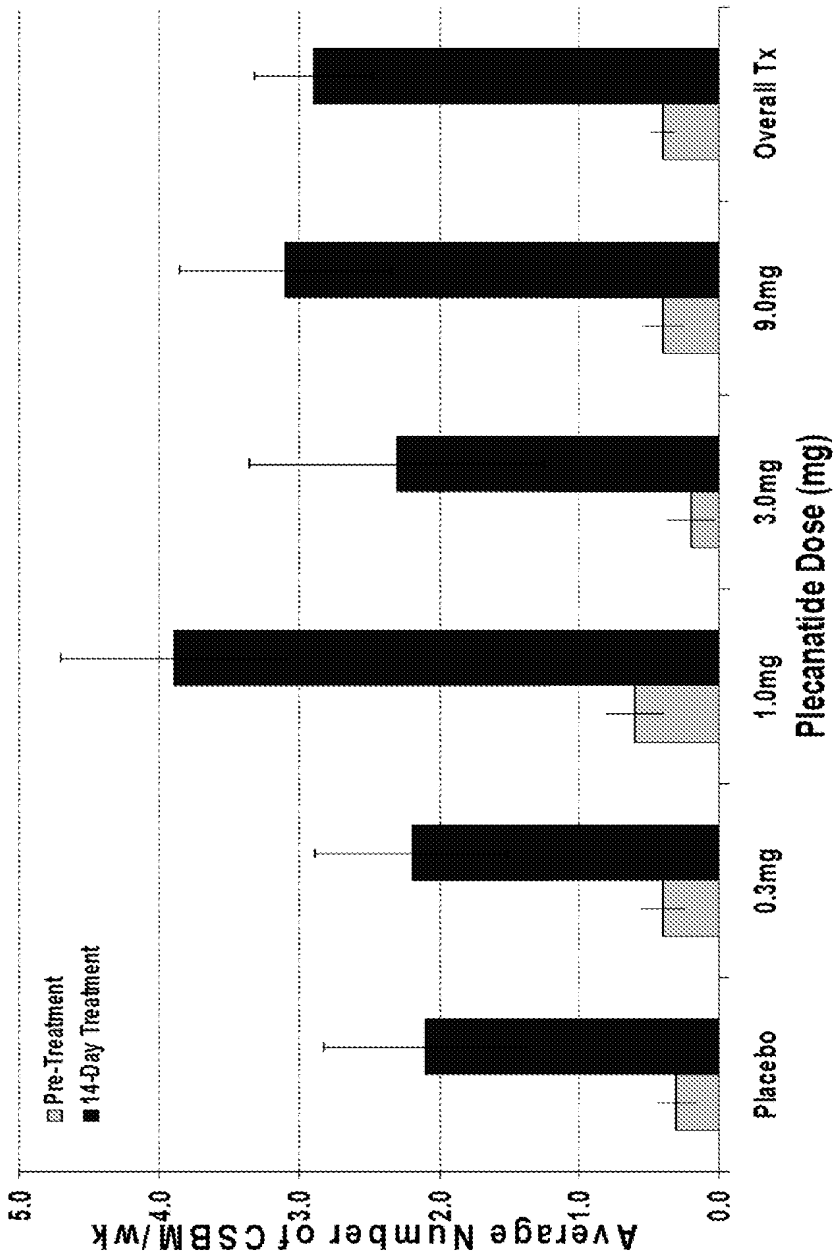
1.0mg
3.0mg
9.0mg
Treatment Groups

Fig. 2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1.0
0.0
Pre-Treatment
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Placebo
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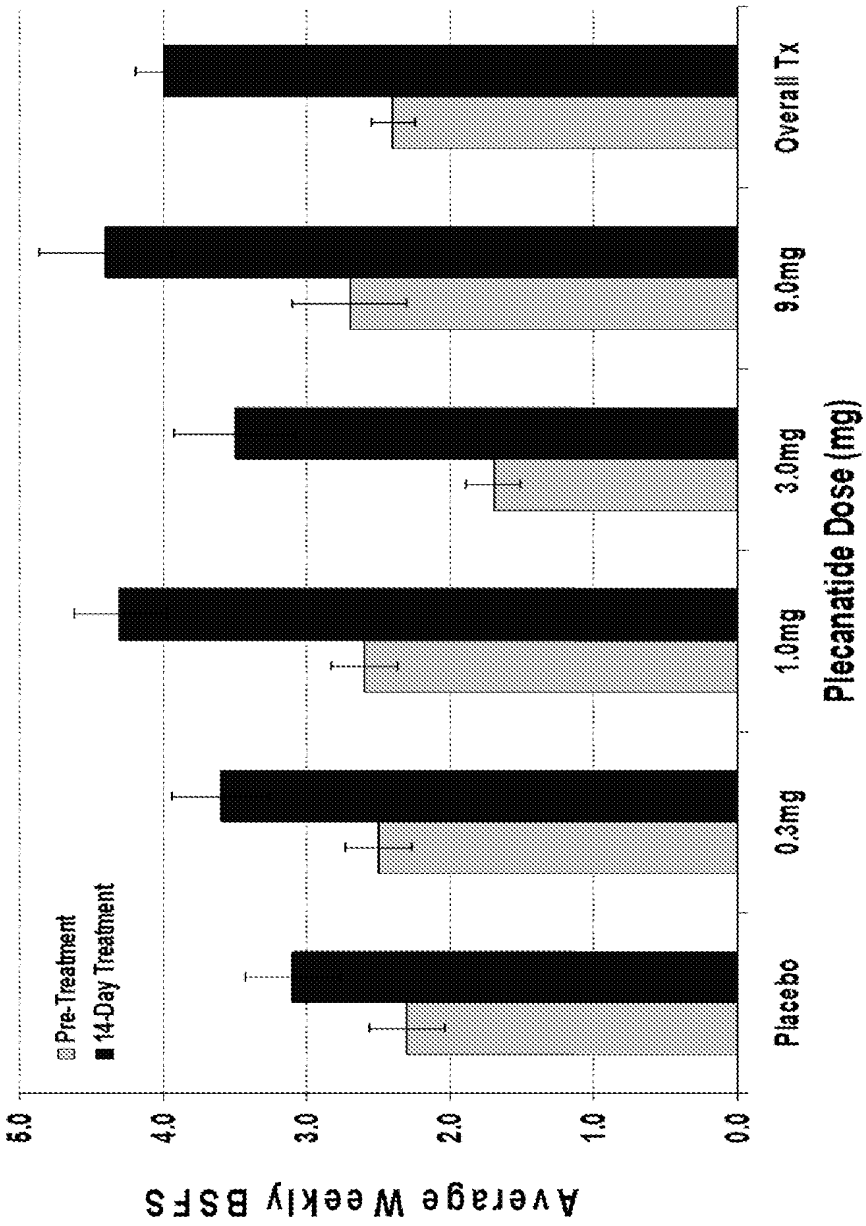
3.0mg
9.0mg
Overall Tx
Plecanatide Dose (mg)

Fig. 3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4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Placebo
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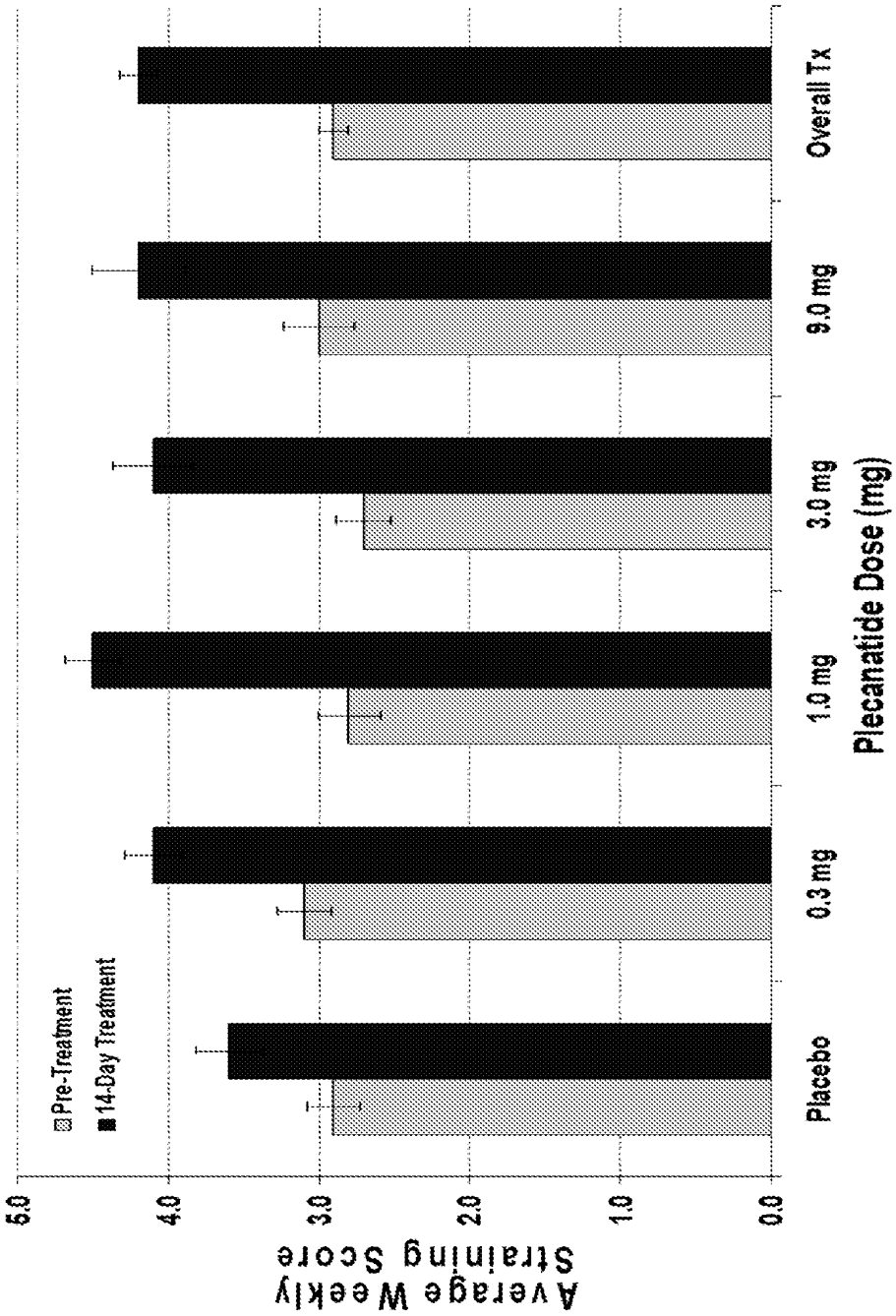
1.0mg
3.0mg
9.0mg
Overall Tx
Plecanatide Dose (mg)

Fig. 4


Average Weekly Straining Score
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4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
Overall Tx
Plecanatide Dose (mg)

Fig. 5

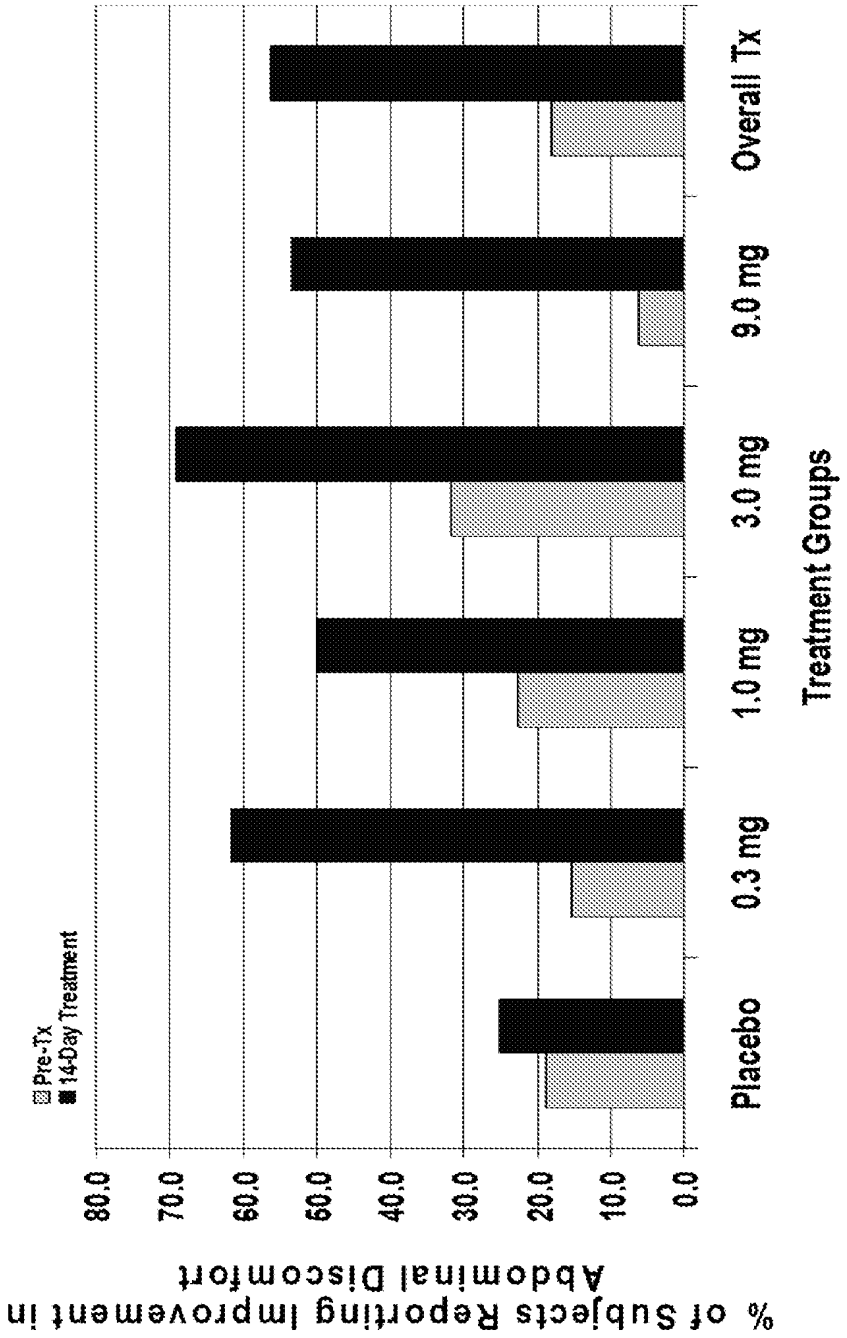
% of Subjects Reporting Improvement in Abdominal Discomfort
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Pre-Tx
14-Day Treatment
Placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
Overall Tx
Treatment Groups

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/030551

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/10 A61P1/00 A61P1/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, Sequence Search, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/020054 A1 (IRONWOOD PHARMACEUTICALS INC [US]; JOHNSTON JEFFREY [US]; KURTZ CAROLI) 17 February 2011 (2011-02-17)	2-42
Y	claims 162,168,170,186,194,195,197,207; sequences 10,13,14	1

Y	WO 2010/065751 A2 (SYNERGY PHARMACEUTICALS INC [US]; SHAILUBHAI KUNWAR [US]; COMISKEY STE) 10 June 2010 (2010-06-10) paragraph [0221]; figure 7; sequences 1,8,9	1

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2013	18/06/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Vandenbogaerde, Ann

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/030551

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAILUBHAI KUNWAR ET AL: "Phase II Clinical Evaluation of SP-304, a Guanylate Cyclase-C Agonist, for Treatment of Chronic Constipation", AMERICAN JOURNAL OF GASTROENTEROLOGY, ELSEVIER SCIENCE INC, US, vol. 105, no. Suppl. 1, 1 October 2010 (2010-10-01), pages S487-S488, XP009152336, ISSN: 0002-9270 abstract --- WO 2012/037380 A2 (SYNERGY PHARMACEUTICALS INC [US]; COMISKEY STEPHEN [US]; FENG RONG [US) 22 March 2012 (2012-03-22) the whole document ---	2-42 1-42
X,P		

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/030551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011020054 A1	17-02-2011	EP 2464373 A1	20-06-2012
		US 2013045239 A1	21-02-2013
		WO 2011020054 A1	17-02-2011
WO 2010065751 A2	10-06-2010	AU 2009322285 A1	30-06-2011
		CA 2745694 A1	10-06-2010
		EP 2373296 A2	12-10-2011
		JP 2012510527 A	10-05-2012
		US 2010221329 A1	02-09-2010
		WO 2010065751 A2	10-06-2010
WO 2012037380 A2	22-03-2012	AU 2011302006 A1	07-03-2013
		CA 2810243 A1	22-03-2012
		US 2012237593 A1	20-09-2012
		WO 2012037380 A2	22-03-2012

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Stephen Comiskey *et al*	Confirmation No.:	3135
Application No.:	13/421,769	Group Art Unit:	1676
Filed:	March 15, 2012	Examiner:	LEE, Jia-Hai

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

EFS
Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT AND RESPONSE

This amendment and response is supplemental to the Response filed on July 4, 2016 and is being filed at the *express request of the Examiner*.

Amendments to the Claims begin on page 2.

Remarks begin on page 6.

Amendments to the Claims:

This listing of claims will replace all prior listings in the application. Please amend the claims as follows.

1. (Canceled)

2. (Canceled)

3. (Currently Amended) The oral dosage formulation of claim [[2]] 45, wherein the GCC agonist peptide has a chromatographic purity of no less than 92% to 95%.

4. (Cancelled)

5. (Currently Amended) The oral dosage formulation of claim [[2]] 45, wherein the formulation is substantially free of inorganic acids and carboxylic acids.

6. (Canceled)

7. (Canceled)

8. (Currently Amended) The oral dosage formulation of claim [[2]] 45, wherein the formulation is a solid formulation and the unit dose is a powder, granule, sachet, troche, tablet, or capsule.

9. -19 (Cancelled).

20. (Currently Amended) The oral dosage formulation of claim [[2]] 45, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

21. (Currently Amended) The oral dosage formulation of claim [[2]] 45, wherein the formulation is in the form of a capsule or tablet.

22. (Original) The oral dosage formulation of claim 21, wherein the capsule or tablet is in a blister pack or strip.

23. -44. (Canceled)

45. (New) An oral dosage formulation consisting of a per unit dose of 3.0 mg or 6.0 mg of a peptide consisting of SEQ ID NO:1, wherein said peptide is a (4,12; 7,15) bicycle, an inert low moisture carrier and a lubricant, wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months.

46. (New) The oral dosage formulation of claim 45, wherein the lubricant is magnesium stearate.

47. (New) The oral dosage formulation of claim 45, wherein the lubricant is at 0.25% (w/w).

48. (New) The oral dosage formulation of claim 45, wherein the inert carrier is microcrystalline cellulose.

49. (New) The oral dosage formulation of claim 45, wherein the inert carrier is at least 96% (w/w).

50. (New) The oral dosage formulation of claim 45, wherein the inert carrier has a particle size of from 50 to 900 microns.

Interview Summary

Provided below is a summary of the telephonic Interview held on September 14, 2016.

The participants in the interview were Jia-Hai Lee (Examiner), Karlheinz R. Skowronek (Examiner Lee's Supervisor),Cynthia Kozakiewicz (Attorney, Cooley LLP), and Ivor Elrifi (Attorney, Cooley LLP).

During the interview, the Examiner requested that the claims in the instant application be amended to the same scope as the formulation recited in the method of use claims in co-pending application 14/845,644. Applicants submit this Supplemental Amendment and Response , according to the Examiner's express request.

REMARKS

Claims 3, 5, 8, 20, 20-22 and 45-50 are pending. Claims 45-50 are new. Claims 1, 2, 4, 6, 7, 9-19 and 23-44 have been canceled without prejudice or disclaimer. Claims 3, 5, 8, 20, and 21, have been amended to correct dependency from new claim 45. Claims 3, 5, 8, 20, 21 and 45-50 are currently under examination. New claims 45-50 recite a formulation of SEQ ID NO:1 , an inert low moisture carrier, and a lubricant. Support for these claims can be found throughout the application as filed, and for example at, original claims 6 (SEQ ID NO:1), 7 (3mg and 6 mg dose) and more specifically according to the table below. No new matter is added.

Claim	Support
45	Para. [017]
46	Para. [017]; claim 18
47	Para. [66]
48	Para. [44]; claim 10
49	Para. [66]
50	Claim 11

The claim amendments presented herein are presented assuming that the amendments made in Applicants July 5, 2016 response had not been entered. With the exception of the claim

amendments, Applicant notes that the arguments presented herein are similar to those presented in the July 5, 2016 Amendment/Response.

Applicants would like to draw to the attention of the Examiner the 37 CFR §1.132 Declaration of Stephan Comiskey (Comiskey Decl.) filed February 19, 2015 in the instant application and the arguments presented in the response filed accompanying the Comiskey Decl. In particular, to ¶¶ 5, 6 and 7 of the Comiskey Decl. stating that formulations with a low moisture carrier as currently claimed were unexpectedly more stable and had less impurity than formulations comprising a regular grade carrier.

Rejection of claims 4 and 9-11 under 35 U.S.C. § 112

The Examiner rejected claims 4 and 9-11 under 35 USC § 112(d) as allegedly being of improper dependent form for failing to further limit the subject matter of the claim from which it depends. Without acquiescing to the correctness of the Examiner's rejection, to further prosecution, Applicants herein cancel claims 4 and 9-11. Accordingly, Applicants respectfully request withdrawal of the instant rejection.

Rejection of claims 2-11, 14-16, 20-23, 25 and 43-44 under 35 U.S.C. § 103

The Examiner rejected claims 2-11, 14-16, 20-23, 25 and 43-44 under 35 U.S.C. § 103(a) as allegedly being obvious over Shailubhai *et al.* (WO 02/078683) in view of Mihranyan *et al.* and Fretzen *et al.* (WO 2010/027404). Office Action at page 5. Claims 2, 4, 6, 7, 9-11, 14-16, 23, 25 and 43-44 have been canceled thus the rejection with respect to those claims is moot. Applicant traverse the rejection as it applies to new independent claim 45 and the claims that depend therefrom.

The Examiner contends Shailubhai *et al.* teach a pharmaceutical composition comprising a GCC agonist peptide with 100% homology to SEQ ID NO:1, where the purity of the GCC agonist peptide is greater than 95%. *Id.* While the Examiner acknowledges Shailubhai does not specify the cellulose carrier is an inert low moisture carrier of cellulose, the Examiner contends Mihranyan teaches the use of low moisture grades of commercial microcrystalline cellulose with moisture-sensitive drugs. *Id.* at pages 5-6. The Examiner concedes that neither Shailubhai nor Mihranyan show peptide purity no less than 91% after storage for at least three months, but contends the skilled artisan would be motivated to combine the disclosure of Shailubhai and

Mihranyan with that of Fretzen *et al.* which teaches GCC agonist peptide formulations that have a chromatographic purity of no less than 91% after 18 or 24 months of storage in a sealed container containing a desiccant at 25°C at 60% relative humidity. *Id.* at page 6.

Applicants respectfully disagree. A *prima facie* case of "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (*citing In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). The present claims are amended to recite the formulation consists of the peptide consisting of SEQ ID NO:1, an inert low moisture carrier, and a lubricant, the peptide has a chromatographic purity of no less than 91% after storage for at least three months. This is neither taught nor suggested in the cited art. Shailubhai does not teach or suggest a formulation consisting of the peptide of SEQ ID NO:1, an inert low moisture carrier, and a lubricant, where the peptide has a chromatographic purity of no less than 91% after storage for at least three months. Nothing in Shailubhai teaches or suggests a formulation with such characteristics. The Examiner has therefore failed to make a *prima facie* case of obviousness.

Nor do Mihranyan or Fretzen cure the deficiencies of Shailubhai. Neither of these references teaches or suggests a formulation consisting of the peptide of SEQ ID NO:1, an inert low moisture carrier, and a lubricant, wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months. In the rejection of claim 16 on page 8 of the instant Office Action, the Examiner argues that Shailubhai teaches peptides of SEQ ID NO:1, Mihranyan suggests the use of inert low moisture grades of commercial MCC, and Fretzen teaches formulations comprising leucine as a peptide stabilizer. However, the skilled artisan would not have combined the art in the manner the Examiner suggests. For example, the formulations disclosed in Fretzen contain a cation and/or an amine (e.g. leucine), neither of which are present in the claimed formulations. Further, given the high stability obtained with the formulations disclosed in Fretzen, the skilled artisan would have had no motivation to replace the various formulation components disclosed therein with an inert low-moisture carrier and a lubricant.

The cited art therefore does not provide a suggestion of all elements of the pending claims. Accordingly, Applicants respectfully request withdrawal of the instant rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees, including those under 37 C.F.R. §§1.16, 1.17, and 1.21, that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: September 14, 2016

Respectfully submitted,

COOLEY LLP

COOLEY LLP
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1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (617) 937-2344
Fax: (202) 842-7899

By: /Cynthia Kozakiewicz/

Cynthia Kozakiewicz
Reg. No. 42,764

136698341 v1

Electronic Acknowledgement Receipt

EFS ID:	26924765
Application Number:	13421769
International Application Number:	
Confirmation Number:	3135
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Customer Number:	58249
Filer:	Cynthia A. Kozakiewicz
Filer Authorized By:	
Attorney Docket Number:	SYPA-009X01US 321994-2142
Receipt Date:	14-SEP-2016
Filing Date:	15-MAR-2012
Time Stamp:	15:44:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Supplemental Response or Supplemental Amendment	SYPA_009_X01US_Suppl_Response.pdf	150480 036ae925c2a3a85d8aea03132c2e143cbb624b42	no	7

Warnings:

Information:	
Total Files Size (in bytes):	150480

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/421,769	Filing Date 03/15/2012	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/14/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 12	Minus	** 44	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
DIANE JOHNSON

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	13/421,769
Filing Date	March 15, 2012
First Named Inventor	Stephen COMISKEY
Title	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/X01US 321994-2142

SIGNATURE of Applicant or Patent Practitioner

Signature	/Anne E. Fleckenstein/	Date (Optional)	September 15, 2016
Name	Anne E. Fleckenstein	Registration Number	62,951
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/82B(07-13)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

58249

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

SYNERGY PHARMACEUTICALS INC.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	Oct. 6, 2014
Name	Gary S. Jacob, Ph.D.		
Title	President and Chief Executive Officer		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

Electronic Acknowledgement Receipt

EFS ID:	26939836
Application Number:	13421769
International Application Number:	
Confirmation Number:	3135
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009X01US 321994-2142
Receipt Date:	15-SEP-2016
Filing Date:	15-MAR-2012
Time Stamp:	16:47:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	SYPA_009_X01US_POA.pdf	346463 6d5b703a58f95bad44b86b604cf391ba6e7f557d	no	2

Warnings:

Information:	
Total Files Size (in bytes):	346463

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142

CONFIRMATION NO. 3135

POA ACCEPTANCE LETTER

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000085950545

Date Mailed: 09/22/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/15/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/dtdinh/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142	3135

58249 7590 10/05/2016

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
LEE, JIA-HAI	

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
10/05/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zpatdcdocketing@cooley.com

Office Action Summary	Application No. 13/421,769	Applicant(s) COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/14/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *3,5,8,20-22 and 45-50* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *3,5,8,20-22 and 45-50* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *12/30/2015,7/5/2016,7/27/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Claim Status

Claims 3, 5, 8, 20-22, and 45-50 are pending.

Claims 1-2, 4, 6-7, 9-19, 20, and 23-44 were canceled.

Claims 3, 5, 8, 20-22, and 45-50 have been examined.

Priority

This application is a CIP of PCT/US2011/051805 filed on 09/15/2011, which claims benefit of 61/383,156 filed on 09/15/2010, claims benefit of 61/387,636 filed on 09/29/2010, and claims benefit of 61/392,186 filed on 10/12/2010. The dosage of 6 mg and chromatographic purity were first disclosed in the PCT/US2011/051805; thus, the prior art date of this application is the effective filing date of PCT/US2011/051805 (09/15/2011) as none of the provisional applications shown as follows disclosed the amended claim 45.

Disclosure	SEQ ID NO: 1	dosage	chromatographic purity
61/383156	Yes	3 mg	no
61/387636	Yes	3 mg [16]	no
61/392186	Yes	3 mg [11]	no

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 12/30/2015,

7/5/2016 and 7/27/2016 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 112

Response to Arguments

The prior rejection of claims 4 and 9-11 under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, is withdrawn in view of application cancelation of the claims.

The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New rejection necessitated by amendment

Claims 5 and 45 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The term "substantially free of" in claim 5 is a relative term which renders the claim indefinite. The term "substantially free of" is not defined by the claim,

the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The term "low moisture carrier" in claim 45 is a relative term which renders the claim indefinite. The term "low moisture carrier" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

Response to Arguments

The prior rejection of claims 2-11, 14-16, 20-23, 25, and 43-44 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Shailubhai et al. (WO 02/078683 A1, cited in the prior action) in view of Mihranyan et al. (Int J Pharm. 2004 Jan 28;269(2):433-42, cited in the prior action) and Fretzen et al. (US 2010/0048489 A1).

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, 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. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

New rejection necessitated by amendment

Claims 3, 8, 21, 45-46, and 48 are rejected under pre-AIA 35 U.S.C.

103(a) as being unpatentable over Currie et al. (WO 2005/016244 A2, recited) in view of FMC biopolymer product (2005, recited), in view of Fretzen et al. (US 2010/0048489 A1, recited) and in view of Shailubhai et al. (Digestive Disease Week. San Diego, 2008, cited in IDS dated 07/05/2016).

Claim 45 is drawn to an oral dosage formulation consisting of (1) a per unit dose of 3.0 mg or 6.0 mg of a peptide consisting a (4, 12; 7, 15) bicyclic SEQ ID NO: 1, (2) an inert low moisture carrier, and (3) a lubricant; wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months.

Currie et al. shows a GC-C receptor agonist peptide (p3, line 7-8; p5, line 1-3) in claim 6 with 100% homology to this instant claim 1 as follows

Claim 6	Asn 1	D/ E	D/ E	C *	Glu 5	Leu 6	C *	Val 8	Asn 9	V/ P	A *	C *	Thr 13	G/ A	C *	Leu 16
SEQ ID NO: 1	N	D	E	C	E	L	C	V	N	V	A	C	T	G	C	L

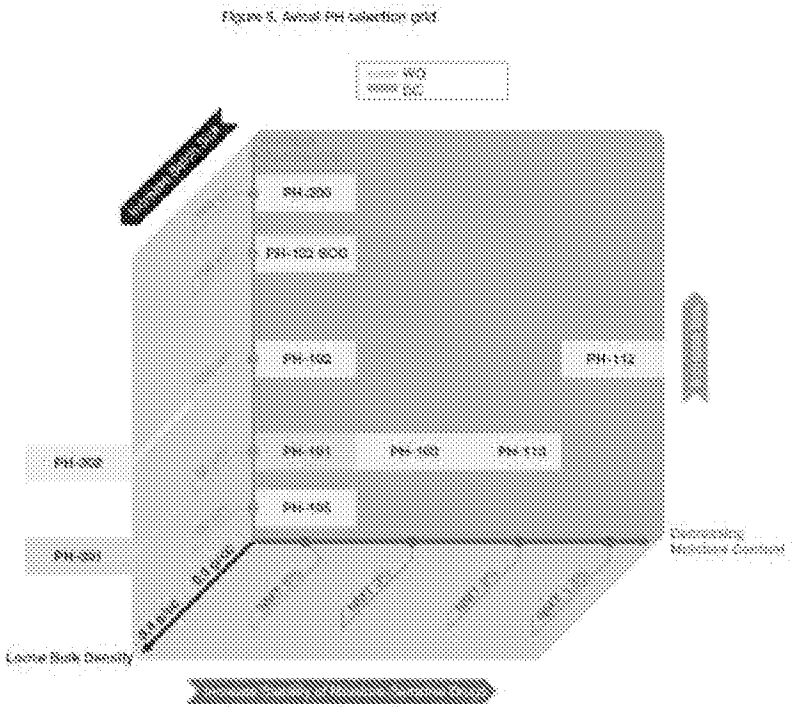
* may be substituted by a non-natural amino acid.

Currie et al. shows when fully folded, disulfide bonds are present between the first and third cysteines and between the second and fourth cysteines, e.g., there is a disulfide bond between Cys4 and Cys12 and a disulfide bond between Xaa7 and Xaa15 (p17, line 29-30 bridging to p18, line 1), reading on a (4, 12; 7, 15) bicyclic SEQ ID NO: 1 in claim 45. Currie et al. shows the therapeutic agent can be administered orally as a capsule or tablet (p7, line 21; p50, line 25-27) and the orally administered compositions can include binders, lubricants (e.g., magnesium stearate at p49, line 5), inert diluents (p51, line 1), reading on lubricant in claim 45. Currie et al. further shows the peptide is formulated with

microcrystalline cellulose (e.g., Avicel PH-103™) purchased from FMC corporation (p48, line 22-23).

Currie et al. does not specify the inert microcrystalline cellulose carrier (p47, line 26-27; p48, line 12-13) purchased from FMC corporation, such as Avicel PH-103™ (p48, line 22-23), is an inert low moisture carrier.

FMC shows a range of low moisture Avice PH grades (e.g., Avice PH-103 or Avice PH-112 and 113) as follows (p12, Fig 5). FMC suggests with proper attention to the kinetics of moisture re-equilibration, you can enjoy the benefits of low-moisture processing without the capital investment of a low-humidity facility (p10, col 1), reading on inert low moisture carrier in claim 45. Thus, one of ordinary skill in the art would enjoy the benefits of low-moisture processing without the capital investment of a low-humidity facility by using the inert low moisture carrier of microcrystalline cellulose sold by FMC as above (p12, Fig 5).



Currie et al. in view of FMC product catalog do not specify the intrinsic

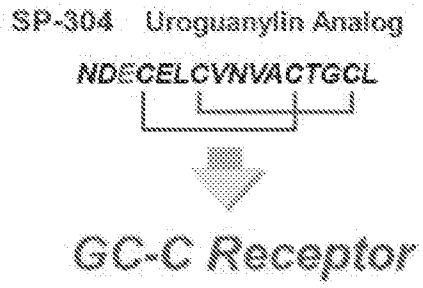
chromatography purity of the peptide stability.

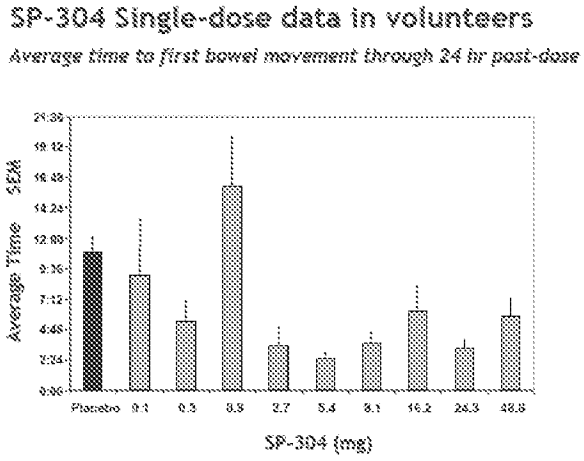
Fretzen et al. teaches an orally administered unit dosage formulation of GC-C receptor agonist polypeptide [0062, claim 274-276] comprising (1) a homolog/analog GC-C receptor agonist polypeptide of SEQ ID NO: 1 (linaclotide), (2) microcrystalline cellulose (e.g. AVICEL™, such as, AVICEL-PH-101™, -103™ and-105™, sold by FMC Corporation) [0052, claim 309, 340, and 396], consistent with Currie et al. described above, and (3) lubricant [0062, claim 303]. Fretzen et al. shows the formulated capsules were placed in plastic bottles containing 1 to 2 g of desiccant and were induction sealed [0097]. The bottles were stored at 40° C/75% RH for six months [0097, table 7]. Fretzen et al. shows the chromatographic purity of the GC-C receptor agonist polypeptide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 18 months or 24 months of storage of the unit dosage form at 25° C. at 60% relative humidity in a sealed container containing a desiccant [0009], reading on the limitation of chromatographic purity no less than 91% in claims 45. It is noted that the difference between Currie's teaching and Fretzen's teaching is a step of storing the tablet or capsule in a sealed container with a desiccant as suggested by Fretzen et al. [0009, 0097]. One of ordinary would have been taught and motivated by Fretzen et al. to store Currie's therapeutic peptide formulation of SEQ ID NO: 1 in a sealed container containing a desiccant [0009] to achieve the chromatographic purity as claimed by Fretzen et al. (claims 274-276) as well as this instant claim 45.

Currie et al. (in view of other combined references) suggests the dosage

of the peptide is orally administered at 1µg/kg- 1mg/kg (p43, line 13), but does not specify a per unit dose of 3.0 mg or 6.0 mg of the peptide.

Shailubhai et al. shows the compound SP-304 consisting of the peptide sequence of SEQ ID NO: 1 taught by Currie et al. as follows. Shailubhai et al. shows no statistical difference for the dosage of SP-304 between 2.7-5.4 mg (rounding up to 3 mg-5 mg) or 5.4-8.1 mg (5mg-8mg), reading on the unit dosage of SEQ ID NO: 1 at 3, 4, 5, 6, 7, or 8 mg and satisfying the unit dose 3 or 6 in claim 45. MPEP 2144.05 states “In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”





With respect to claims 3 and 20, Fretzen et al. shows the chromatographic purity of the GC-C receptor agonist polypeptide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 18 months or 24 months of storage of the unit dosage form at 25° C. at 60% relative humidity in a sealed container containing a

desiccant [0009, 0097], reading on claim 20. One of ordinary would have been taught by Fretzen et al. to store Currie's peptide formulation of SEQ ID NO: 1 in a sealed container containing a desiccant [0009, 0097] to achieve the claimed chromatographic purity.

With respect to claims 8 and 21, Currie et al. shows the therapeutic agent can be administered orally as a capsule of tablet (p7, line 21; p50, line 25-27).

With respect to claim 22, Fretzen et al. shows a GC-C receptor agonist polypeptide is in unit dosage form of a capsule or a tablet may be obtained in a container and in the alternative a blister pack can be used with individual doses for pressing out of the pack according to a therapeutic schedule [0072].

With respect to claim 46, Currie et al. shows the therapeutic agent administered orally as a capsule comprising a lubricant of magnesium stearate (p49, line 5).

With respect to claim 48, Currie et al. shows the inert carrier is microcrystalline cellulose (e.g., Avicel PH-103^{TM}) purchased from FMC corporation (p48, line 22-23).

With respect to claim 50, FMC catalog shows the particle size of Avicel PH-103^{TM} is 50 µm (p6, Table).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Currie's peptide formulation with FMC's microcrystalline cellulose because Currie et al. shows the therapeutic peptide of this instant SEQ ID NO: 6 (claim 6) is formulated with microcrystalline cellulose (e.g., Avicel PH-103^{TM}) purchased from FMC corporation (p48, line 22-23) and

FMC suggests with proper attention to the kinetics of moisture re-equilibration, you can enjoy the benefits of low-moisture processing without the capital investment of a low-humidity facility (p10, col 1). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings (Currie et al. in view of FMC's catalog) with Fretzen's teaching of maintaining chromatographic purity of a GC-C receptor agonist polypeptide because Currie et al. in view of FMC's catalog teach an oral dosage of a GC-C receptor agonist polypeptide formulation and Fretzen et al. suggests the GC-C receptor agonist polypeptide formulation (e.g., tablet or capsule) to be stored in a sealed container containing a desiccant to maintain the chromatographic purity of the GC-C receptor agonist polypeptide greater than 98% (less than 2% degradation) [0006-0009; claim 274]. It would have been further obvious to combine the teachings (Currie et al. in view of FMC product catalog and Fretzen et al.) with Shailubhai's teaching of SP-304 because Shailubhai et al. shows no statistical difference for the dosage of SP-304 between 2.7 mg (rounding up to 3 mg) and 8.1 mg, suggesting all dosages in the range between 2.7-8.1 mg are effective for their therapeutic use. The combination would have reasonable expectation of success. MPEP 2144.05 states "In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)."

Response to Arguments

Applicant's arguments filed 09/14/2016 have been fully considered but they are not persuasive because applicant argues Shailubhai *et al.* (WO 02/078683) in view of Mihranyan *et al.* and Fretzen *et al.* (WO 2010/027404), but the argument does not apply to the new grounds of rejection Currie et al. (WO 2005/016244 A2, recited) in view of FMC biopolymer product (2005, recited), in view of Fretzen et al. (US 2010/0048489 A1, recited) and in view of Shailubhai et al. (Digestive Disease Week. San Diego, 2008, cited in IDS dated 07/05/2016). See the rejection above in details.

New rejection necessitated by amendment

Claims 45 and 47 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al. and Shailubhai et al. as applied to claims 3, 8, 20-22, 45-46, 48, 50 and further in view of Chen et al. (WO 2007/106468 A2).

Claim 47 is drawn to the lubricant is at 0.25% (w/w).

Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al. and Shailubhai et al. teach an oral dosage tablet formulation comprising lubricant (e.g., magnesium stearate).

Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al. and Shailubhai et al. do not specify the amount of lubricant in the oral dosage tablet formulation.

Chen et al. teach oral tablet formulation of therapeutic agent comprising a moisture barrier coating (p10, line 16-17). Chen et al. teach the tablet contains a

lubricant such as magnesium stearate is optimized from about 0.1 % to about 8% of the total weight of the composition (p16, line 8-10), reading on 0.25% (w/w) in claim 47. MPEP 2144.05 states “In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings (Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al. and Shailubhai et al.) with Chen’s teaching of lubricant for oral tablet formulation because Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al. and Shailubhai et al. teach an oral peptide tablet/capsule formulation comprising lubricant (such as magnesium stearate See Currie et al. p49, line 5) and Chen et al. suggest lubricant (such as magnesium stearate) in a tablet is optimized from about 0.1 % to about 8% of the total weight of the composition (p16, line 8-10). The combination would have reasonable expectation of success. MPEP 2144.05 states “In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”

Response to Arguments

Applicant's arguments filed 09/14/2016 have been fully considered but they are not persuasive. See response to argument above.

New rejection necessitated by amendment

Claims 45 and 5 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al., in view of Shailubhai et al. and in view of Chen et al. as applied to claims 3, 8, 20-22, 45-48, 50 and further in view of Schaible et al. (US 2005/0145351 A1).

Claim 5 is drawn to the oral dosage formulation is substantially free of inorganic acids and carboxylic acids.

Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al., in view of Shailubhai et al. and in view of Chen et al. teach an oral dosage peptide formulation comprising microcrystalline cellulose.

Currie et al. in view of FMC biopolymer catalog, in view of Fretzen et al., in view of Shailubhai et al. and in view of Chen et al. do not teach an oral dosage peptide formulation is substantially free of inorganic acids and carboxylic acids.

Schaible et al. teach a process of producing microcrystalline cellulose (Abstract, claim 34). Schaible et al. shows microcrystalline cellulose is hydrolyzed by hydrochloric acid (reading on inorganic acid) [0060] and an organic carboxylic acid e.g., acetic acid (claim 40 and 54). Thus, one of ordinary skill in the art would make an oral dosage peptide formulation substantially free of inorganic acids and carboxylic acids to prevent the microcrystalline cellulose from degradation by acids.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings (Currie et al. in view of FMC

biopolymer catalog, in view of Fretzen et al., in view of Shailubhai et al. and Chen et al.) with Schaible's teaching of microcrystalline cellulose because Schaible et al. shows microcrystalline cellulose is hydrolyzed by hydrochloric acid (reading on inorganic acid) [0060] and an organic carboxylic acid e.g., acetic acid (claim 40 and 54). Thus, one of ordinary skill in the art would make an oral dosage peptide formulation substantially free of inorganic acids and carboxylic acids to prevent microcrystalline cellulose from degradation by acids. The combination would have reasonable expectation of success.

Response to Arguments

Applicant's arguments filed 09/14/2016 have been fully considered but they are not persuasive. See response to argument above.

Claims 45 and 49 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Currie et al. (WO 2005/016244 A2, recited) in view of Yang et al. (US 5,817,624), in view of Fretzen et al. (US 2010/0048489 A1, recited) and in view of Shailubhai et al. (Digestive Disease Week. San Diego, 2008, cited in IDS dated 07/05/2016).

Claim 45 is drawn to an oral dosage formulation consisting of (1) a per unit dose of 3.0 mg or 6.0 mg of a peptide consisting a (4, 12; 7, 15) bicyclic SEQ ID NO: 1, (2) an inert low moisture carrier, and (3) a lubricant; wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three

months.

Currie et al. shows a GC-C receptor agonist peptide (p3, line 7-8; p5, line 1-3) in claim 6 with 100% homology to this instant claim 1 as follows

Claim 6	Asn 1	D/ E	D/ E	C *	Glu 5	Leu 6	C *	Val 8	Asn 9	V/ P	A *	C *	Thr 13	G/ A	C *	Leu 16
SEQ ID NO: 1	N	D	E	C	E	L	C	V	N	V	A	C	T	G	C	L

* may be substituted by a non-natural amino acid.

Currie et al. shows when fully folded, disulfide bonds are present between the first and third cysteines and between the second and fourth cysteines, e.g., there is a disulfide bond between Cys4 and Cys12 and a disulfide bond between Xaa7 and Xaa15 (p17, line 29-30 bridging to p18, line 1), reading on a (4, 12; 7, 15) bicyclic SEQ ID NO: 1 in claim 45. Currie et al. shows the therapeutic agent can be administered orally as a capsule or tablet (p7, line 21; p50, line 25-27) and the orally administered compositions can include inert lubricant such as mineral oil (p47, line 25-27; p48, line 13; p49, line 5), reading on lubricant in claim 45.

Currie et al. does not specify mineral oil is an intrinsic inert carrier.

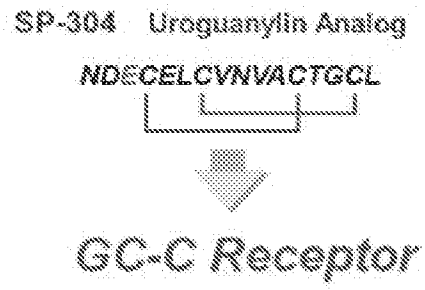
Yang et al. shows a pharmaceutical formulation for the oral delivery of a therapeutic polypeptide comprising a pharmaceutically acceptable oil (claim 1), reading a pharmaceutical acceptable carrier. Yang et al. shows the pharmaceutically acceptable oil/carrier is mineral oil and the weight percentage of mineral oil is in an amount of 50%-99% w/w (claims 2-3), reading on both an inert low moisture carrier and lubricant (taught by Currie et al.) in claim 45.

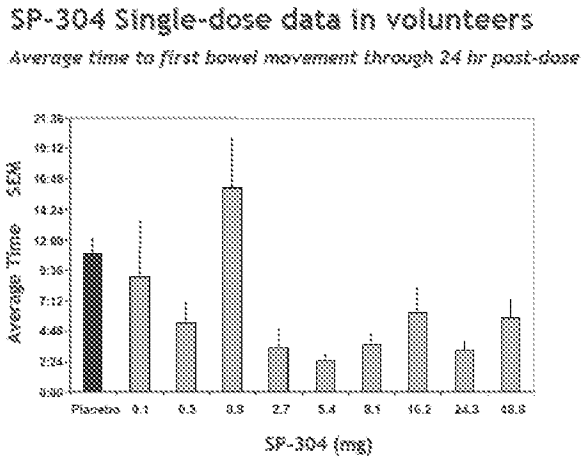
Currie et al. in view of Yang et al. do not specify the intrinsic chromatography purity of the peptide stability.

Fretzen et al. teaches an orally administered unit dosage formulation of GC-C receptor agonist polypeptide [0062, claim 274-276]. Fretzen et al. shows the formulated capsules were placed in plastic bottles. The bottles contained 1 to 2 g of desiccant and were induction sealed. The bottles were stored at 40° C/75% RH for six months [0097, table 7]. Fretzen et al. shows the chromatographic purity of the GC-C receptor agonist polypeptide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 18 months or 24 months of storage of the unit dosage form at 25° C. at 60% relative humidity in a sealed container containing a desiccant [0009], reading on the limitation of chromatographic purity no less than 91% in claims 45.

Currie et al. (in view of other combined references) suggests the dosage of the peptide is orally administered at 1µg/kg- 1mg/kg (p43, line 13), but does not specify a per unit dose of 3.0 mg or 6.0 mg of the peptide.

Shailubhai et al. shows the compound SP-304 consisting of the peptide sequence of SEQ ID NO: 1 taught by Currie et al. as follows. Shailubhai et al. shows no statistical difference for the dosage of SP-304 between 2.7 mg (rounding up to 3 mg) and 8.4 mg, reading on the unit dosage of SEQ ID NO: 1 at 3, 4, 5, 6, 7, or 8 mg and satisfying the unit dose 3 or 6 in claim 45. MPEP 2144.05 states “In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”





With respect to claim 49, Yang et al. shows an alternative pharmaceutical formulation for the oral delivery of a therapeutic polypeptide comprising a pharmaceutically acceptable inert mineral oil in an amount of 50%-99% w/w (claims 2-3). MPEP 2144.05 states “In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Currie’s oral peptide formulation with Yang’s mineral oil because Currie’s oral peptide formulation comprising inert mineral oil as lubricant (p47, line 25-27; p48, line 13; p49, line 5) and Yang et al. suggests the use of mineral oil at an amount of 50%-99% w/w (claims 2-3) as an alternative pharmaceutical formulation for the oral delivery of a therapeutic polypeptide (claim 1). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings (Currie et al. in

view of Yang et al.) with Fretzen's teaching of maintaining chromatographic purity of a GC-C receptor agonist polypeptide because Currie et al. in view of Yang et al. teach an oral dosage of a GC-C receptor agonist polypeptide formulation and Fretzen et al. suggests the GC-C receptor agonist polypeptide formulation (e.g., tablet or capsule) stored in a sealed container containing a desiccant to maintain the chromatographic purity of the GC-C receptor agonist polypeptide greater than 98% (less than 2% degradation) [0006-0009]. It would have been further obvious to combine the teachings (Currie et al. in view of Yang et al. and Fretzen et al.) with Shailubhai's teaching of SP-304 because Shailubhai et al. shows no statistical difference for the dosage of SP-304 between 2.7 mg (rounding up to 3 mg) and 8.1 mg, suggesting all dosages in the range between 2.7-8.1 mg are effective for their therapeutic use. The combination would have reasonable expectation of success. MPEP 2144.05 states "In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)."

Response to Arguments

Applicant's arguments filed 09/14/2016 have been fully considered but they are not persuasive. See response to argument above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached on Mon-Fri from 9:00 A.M. to 5:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on 571-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./
Examiner, Art Unit 1676

/KARLHEINZ R SKOWRONEK/
Supervisory Patent Examiner, Art Unit 1676

23-September-2016

Notice of References Cited	Application/Control No. 13/421,769	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2005/0145351 A1	07-2005	Schaible, David	C08B15/02	162/9
*	B	US-5,817,624 A	10-1998	Yang; Heechung	A61K9/4858	514/11.4
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO2007106468A2	09-2007	US	Chen et al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/SB/08a (09-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT LIST

(Use as many sheets as necessary)

Complete if Known	
Application Number	13/421,769
Filing Date	March 15, 2012
First Named Inventor	Stephen Comiskey
Art Unit	1676
Examiner Name	Jia-Hai Lee
Attorney Docket Number	SYPA-009/X001US 321994-2142

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
/J.L/	1.	JP 2009-519343 A (corresponds to WO 2007/070562 A2)	05-14-2009			✓
/J.L/	2.	JP 2009-537535 A (corresponds to WO 2007/133796 A2)	10-29-2009			✓
/J.L/	3.	JP 2010-519217 A (corresponds to WO 2008/102264 A2)	06-03-2010			✓
/J.L/	4.	WO 2007/070562 A2	06-21-2007	HARKNESS PHARMACEUTICALS, INC.		
/J.L/	5.	WO 2007/133796 A2	11-22-2007	ENCYSIVE PHARMACEUTICALS, INC.		
/J.L/	6.	WO 2008/102264 A2	08-28-2008	EURAND PHARMACEUTICALS LIMITED		

Examiner Signature:		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08a (09-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT LIST

(Use as many sheets as necessary)

Complete if Known	
Application Number	13/421,769
Filing Date	March 15, 2012
First Named Inventor	Stephen Comiskey
Art Unit	1676
Examiner Name	Jia-Hai Lee
Attorney Docket Number	SYPA-009/X001US 321994-2142

NON PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
/J.L/	7.	SHAILUBHAI et al., "A randomized, double-blind, u placebo-controlled, single-, ascending-, oral-dose safety, tolerability and pharmacokinetic study of SP-304 in healthy adult human male and female volunteers." Digestive Disease Week. San Diego: 2008.	

Examiner Signature:	/JIA-HAI LEE/	Date Considered	09/16/2016

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L78	115	(Stephen near3 Comiskey).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L79	4	L78 and (Oral dosage)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L80	280	(Rong near3 Feng).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L81	9	L80 and (oral)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L82	136	(John near3 Foss).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L83	3	L82 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L84	217	(Kunwar near3 Shailubhai).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L85	64	L84 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L86	48	L85 and arginine	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L87	2	peptide same (liquid formulation) same (blister pack)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55

L88	124	(liquid formulation) same (blister pack)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L89	90	L88 and peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L90	34	L89 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L91	8226	guanylate cyclase	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L92	6	L88 and L91	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L93	281	L91 and (liquid formulation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L94	77	L93 and blister	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L95	28	L94 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L96	62	L93 AND ((A61K2300/00 OR A61K38/10 OR A61K31/215 OR A61K8/731 OR C07D213/81 OR C07D213/56).CPC.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L97	19	(low near moisture near carrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L98	44	(synergy near2 pharmaceuticals).asn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L99	35	L98 and L54	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55

L100	821130	lubricant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L101	867188	oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L102	796816	peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/09/22 20:55
L103	271064	magnesium with stearate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/09/22 20:55
L104	678	L100 same L101 same L102	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/09/22 20:55
L105	303	L104 and @py<"2011"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/09/22 20:55
L106	334	L103 same L104	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/09/22 20:55
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/421,769
Filing Date	March 15, 2012
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3] "Number[4] "Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 2

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
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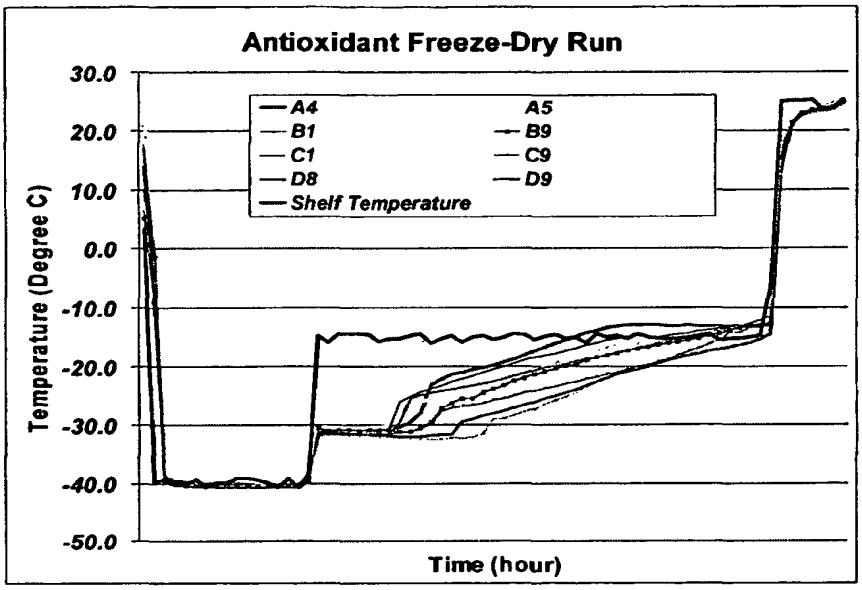
(54) Title: FORMULATIONS OF SITAXSENTAN SODIUM



(57) Abstract: Provided herein are stable lyophilized and oral formulations of sitaxsentan sodium. In certain embodiments the lyophilized formulations provided herein have improved stability upon reconstitution. Also provided are methods of making and using the formulations.

WO 2007/106468 A2

FORMULATIONS OF SITAXSENTAN SODIUM

This application claims priority to U.S. provisional application Serial No. 60/781,880 filed March 13, 2006, entitled "FORMULATIONS OF SITAXSENTAN SODIUM" to Chen *et al.* The disclosure of the above referenced application is incorporated by reference herein.

FIELD

Provided herein are formulations of sitaxsentan sodium and methods for treating endothelin-mediated disorders using the same. In certain embodiments, provided herein are lyophilized formulations. In certain embodiments, the formulations are oral tablets. Also provided are methods of making and using the formulations.

BACKGROUND

Sitaxsentan sodium modulates activity of the endothelin family of peptides and is useful for the treatment of endothelin-mediated disorders. Due to the nature of these disorders, formulations containing sitaxsentan sodium may require storage for an extended period of time. In case of lyophilized powders, stability of the reconstituted formulations is important. The previously known lyophilized formulations of sitaxsentan sodium are not stable upon reconstitution. Therefore, stable formulations of this compound are desired.

SUMMARY

In one embodiment, provided herein are lyophilized formulations of sitaxsentan sodium and methods for treatment of endothelin mediated disorders using the same. The formulations contain one or more antioxidants to prevent oxidation of sitaxsentan sodium. In one embodiment, the antioxidant is monothioglycerol, ascorbic acid, sodium bisulfite or sodium sulfite or a combination thereof. The formulations optionally further contain a buffer and/or a bulking agent, selected from sugars, polyalcohols, amino acids, polymers and polysaccharides.

In one embodiment, provided herein are oral tablet formulations of sitaxsentan sodium and methods for treatment of endothelin mediated disorders using the same. The tablets contain one or more excipients selected from a buffer, an antioxidant, a binding agent, a diluent, a lubricant and a coating agent.

Also provided are methods of making the formulations. Further provided are articles of manufacture containing packaging material, the stable formulation of

sitaxsentan sodium and a label that indicates that the formulation is for the treatment of an endothelin mediated disorder.

BRIEF DESCRIPTION OF FIGURES

Figure 1 demonstrates small scale lyophilization of sitaxsentan sodium formulation containing various antioxidant systems (Formulas 1A to 4A described in the examples correspond to samples in the figure as follows: IVA = A; IIA = B; IA = C; IIIA = D).

Figure 2 demonstrates lyophilization of 25mg/mL sitaxsentan sodium in 20mM citrate buffer (pH 6), 4% dextrose with 2mg/mL ascorbic acid, 6.6mg/mL sodium bisulfite, and 2mg/mL sodium sulfite for prototype stability.

Figure 3 demonstrates lyophilization of 25mg/mL sitaxsentan sodium in 20mM citrate buffer (pH 7) 4% dextrose with 10mg/mL monothioglycerol.

Figure 4 demonstrates lyophilization of 25mg/mL sitaxsentan sodium in 20mM phosphate buffer (pH 7), 4% dextrose with 10mg/mL monothioglycerol for prototype stability.

Figure 5 illustrates lyophilization conditions for formulations 8a, 8b and 8c.

DETAILED DESCRIPTION

A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein "sitaxsentan" refers to N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]-thiophene-3-sulfonamide. Sitaxsentan is also known as TBC11251. Other chemical names for sitaxsentan include 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methylphenylacetyl]-thiophene-3-sulfonamide. The chemical structures of sitaxsentan and sitaxsentan sodium salt are described elsewhere herein.

As used herein "subject" is an animal, such as a mammal, including human, such as a patient.

As used herein, "an endothelin-mediated disorder" is a condition that is caused by abnormal endothelin activity or one in which compounds that inhibit endothelin activity have therapeutic use. Such disorders include, but are not limited to hypertension, cardiovascular disease, asthma, inflammatory diseases, ophthalmologic disease, menstrual disorders, obstetric conditions, gastroenteric disease, renal failure, pulmonary hypertension, endotoxin shock, anaphylactic shock, or hemorrhagic shock.

As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a patient is suffering from the specified disease or disorder, which reduces the severity of the disease or disorder, or retards or slows the progression of the disease or disorder. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating pulmonary hypertension.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, unless otherwise specified, the terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a patient begins to suffer from the specified disease or disorder, which inhibits or reduces the severity of the disease or disorder.

As used herein, and unless otherwise indicated, the terms "manage," "managing" and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

As used herein, and unless otherwise specified, the terms "therapeutically effective amount" and "effective amount" of a compound mean an amount sufficient to provide a therapeutic benefit in the treatment, prevent and/or management of a disease, to delay or minimize one or more symptoms associated with the disease or disorder to be treated. The terms "therapeutically effective amount" and "effective amount" can

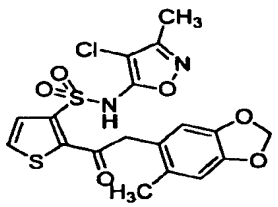
encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or disorder, or enhances the therapeutic efficacy of another therapeutic agent.

As used herein, and unless otherwise specified, the term "prophylactically effective amount" of a compound means an amount sufficient to prevent a disease or disorder, or one or more symptoms associated with the disease or disorder, or prevent its recurrence. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

The terms "co-administration" and "in combination with" include the administration of two therapeutic agents either simultaneously, concurrently or sequentially with no specific time limits. In one embodiment, both agents are present in the cell or in the patient's body at the same time or exert their biological or therapeutic effect at the same time. In one embodiment, the two therapeutic agents are in the same composition or unit dosage form. In another embodiment, the two therapeutic agents are in separate compositions or unit dosage forms. In some embodiments, a first agent can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent.

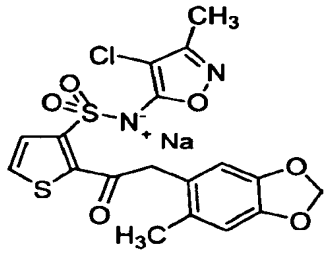
B. Sitaxsentan sodium

The chemical name for sitaxsentan is N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]-thiophene-3-sulfonamide, and its structural formula is as follows:



Sitaxsentan

Sitaxsentan sodium has the formula:



Sitaxsentan, sodium

Sitaxsentan sodium is a potent endothelin receptor antagonist that has oral bioavailability in several species, a long duration of action, and high specificity for ETA receptors.

C. Exemplary Formulations

Provided herein are lyophilized and oral tablet formulations of sitaxsentan sodium.

Lyophilized Formulations

In certain embodiments, provided herein are lyophilized powder formulations of sitaxsentan sodium. In one embodiment, the lyophilized powder contains an antioxidant, a buffer and a bulking agent. In the lyophilized powders provided herein, the amount of sitaxsentan sodium present is in a range from about 25% to about 60% by total weight of the lyophilized powder. In certain embodiments, the amount of sitaxsentan sodium is from about 30% to about 50 % or about 35% to about 45% by total weight of the lyophilized powder. In certain embodiments, the amount of sitaxsentan sodium is about 30%, 33%, 35%, 37%, 40%, 41%, 43%, 45%, 47%, 50%, 53%, 55% or 60% by total weight of the lyophilized powder. In one embodiment, the amount of sitaxsentan sodium in the lyophilized powder is about 41% by total weight of the lyophilized powder.

In certain embodiments, the lyophilized powder contains an antioxidant, such as sodium sulfite, sodium bisulfite, sodium metasulfite, monothioglycerol, ascorbic acid or a combination thereof. In one embodiment, the antioxidant is monothioglycerol. In one embodiment, the antioxidant is a combination of ascorbic acid, sodium sulfite and sodium bisulfite. In certain embodiments, the lyophilized formulations provided herein

have improved stability upon reconstitution as compared to the known lyophilized formulations of sitaxsentan sodium (see WO 98/49162).

In certain embodiments, the antioxidant is monothioglycerol. In certain embodiments, the monothioglycerol is present in an amount ranging from about 10% to about 30% by total weight of the lyophilized powder. In certain embodiments, the monothioglycerol is present in an amount ranging from about 12% to about 25% or about 15% to about 20% by total weight of the lyophilized powder. In certain embodiments, the amount of monothioglycerol in the lyophilized powder is about 10%, 12%, 14%, 15%, 15.5%, 16%, 16.2%, 16.4%, 16.8%, 17%, 17.5%, 19%, 22%, 25% or 30% by total weight of the lyophilized powder. In certain embodiments, the amount of monothioglycerol is about 16.4% by total weight of the lyophilized powder.

In certain embodiments, the sodium sulfite is present in an amount from about 1% to about 6% by total weight of the lyophilized powder. In other embodiments, the sodium sulfite is present in an amount from about 1.5% to about 5% or about 2% to about 4%. In certain embodiments, the amount of sodium sulfite is about 1%, 1.5%, 2%, 2.5%, 3%, 3.3%, 3.5%, 3.8%, 4%, 4.5% or 5% by total weight of the lyophilized powder. In one embodiment, the amount of sodium sulfite is about 3.3% by total weight of the lyophilized powder.

In certain embodiments, the ascorbic acid is present in an amount from about 1% to about 6% by total weight of the lyophilized powder. In other embodiments, the ascorbic acid is present in an amount from about 1.5% to about 5% or about 2% to about 4%. In certain embodiments, the amount of ascorbic acid is about 1%, 1.5%, 2%, 2.5%, 3%, 3.3%, 3.5%, 3.8%, 4%, 4.5% or 5% by total weight of the lyophilized powder. In one embodiment, the amount of ascorbic acid is about 3.3% by total weight of the lyophilized powder.

In certain embodiments, the sodium bisulfite is present in an amount from about 5% to about 15% or about 8% to about 12% by total weight of the lyophilized powder. In certain embodiments, the sodium bisulfite is present in an amount from about 5%, 6%, 7%, 8%, 9%, 10%, 10.3%, 10.5%, 10.8%, 11%, 11.5%, 12% or 15% by total weight of the lyophilized powder. In one embodiment, the amount of sodium bisulfite is about 10.8% by total weight of the lyophilized powder.

In one embodiment, the antioxidant is a combination of ascorbic acid, sodium sulfite and sodium bisulfite. In one embodiment, the amount of ascorbic acid in the lyophilized powder is about 3.3%, the amount of sodium sulfite is about 3.3% and the amount of sodium bisulfite is about 10.8% by total weight of the lyophilized powder

In one embodiment, the lyophilized powder also contains one or more of the following excipients: a buffer, such as sodium or potassium phosphate, or citrate buffer; and a bulking agent, such as glucose, dextrose, maltose, sucrose, lactose, sorbitol, mannitol, glycine, polyvinylpyrrolidone or dextran. In one embodiment, the bulking agent is selected from dextrose, D-mannitol and sorbitol.

In certain embodiments, the lyophilized powders provided herein contain a phosphate buffer. In certain embodiments, the phosphate buffer is present in a concentration of about 10 mM, about 15 mM, about 20 mM, about 25 mM or about 30 mM. In certain embodiments, the phosphate buffer is present in a concentration of 20 mM. In certain embodiments, the phosphate buffer is present in a concentration of 20 mM, and the constituted formulation has a pH of about 7.

In certain embodiments, the lyophilized powders provided herein contain a citrate buffer. In one embodiment, the citrate buffer is sodium citrate dihydrate. In certain embodiments, the amount of sodium citrate dihydrate is from about 5% to about 15%, about 6% to about 12% or about 7% to about 10% by total weight of the lyophilized powder. In certain embodiments, the amount of sodium citrate dihydrate in the lyophilized powder is about 5%, 6%, 7%, 7.5%, 8%, 8.3%, 8.5%, 8.8%, 9%, 9.5%, 10%, 12% or about 15% by total weight of the lyophilized powder. In certain embodiments, the constituted formulation has a pH of about 5 to 10, or about 6.

In certain embodiments, the lyophilized powder provided herein contains dextrose in an amount ranging from about 30% to about 60% by total weight of the lyophilized powder. In certain embodiments, the amount of dextrose is about 30%, 35%, 40%, 45%, 50% or 60% by total weight of the lyophilized powder. In certain embodiments, the amount of dextrose is about 40% by total weight of the lyophilized powder. In certain embodiments, the lyophilized powder provided herein contains mannitol in an amount ranging from about 20% to about 50% by total weight of the lyophilized powder. In certain embodiments, the amount of mannitol is about 20%, 25%, 30%, 32%, 32.5%, 32.8%, 33%, 34%, 37%, 40%, 45% or 50% by total weight of

the lyophilized powder. In certain embodiments, the amount of mannitol is about 32.8% by total weight of the lyophilized powder.

In certain embodiments, the lyophilized powder provided herein contains about 41% of sitaxsentan sodium, about 3.3% ascorbic acid, about 3.3% sodium sulfite and about 10.8% mg sodium bisulfite, about 8.8% sodium citrate dihydrate and about 32.8% D-mannitol by total weight of the lyophilized powder. In certain embodiments, the lyophilized powder has the following composition:

Sitaxsentan Sodium Lyophilized Formulation

Component	Quantity in a 10 mL vial (mg/vial)
Sitaxsentan Sodium	250.0
Sodium Citrate Dihydrate	53.5
L-Ascorbic Acid	20.0
D-Mannitol	200.0
Sodium Bisulfite	66.0
Sodium Sulfite	20.0
Sodium Hydroxide or Hydrochloride Acid	QS to pH 6

In certain embodiments, the lyophilized powder provided herein contains about 40 to about 30% of sitaxsentan sodium, about 4 to about 6% ascorbic acid, about 6 to about 8% sodium citrate dihydrate, about 50 to about 60% D-mannitol and about 1 to about 2% citric acid monohydrate by total weight of the lyophilized powder. In certain embodiments, the lyophilized powder provided herein contains about 33% of sitaxsentan sodium, about 5.3% ascorbic acid, about 7.6% sodium citrate dihydrate, about 53% D-mannitol and 0.13% citric acid monohydrate by total weight of the lyophilized powder. In one embodiment, the lyophilized powder has the following composition:

Sitaxsentan Sodium Lyophilized Formulation

Component	Quantity in a 10 mL vial (mg/vial)
Sitaxsentan Sodium	250.0
Sodium Citrate Dihydrate	57.1
L-Ascorbic Acid	40.0
D-Mannitol	400.0
Citric Acid Monohydrate	1.3
Sodium Hydroxide or Hydrochloride Acid	QS to pH 6.8

In certain embodiments, the lyophilized powder provided herein contains about 40 to about 30% of sitaxsentan sodium, about 4 to about 6% ascorbic acid, about 3 to about 4% sodium phosphate dibasic heptahydrate, about 50 to about 60% D-mannitol and about 1.5 to about 2.5% sodium phosphate monobasic monohydrate by total weight of the lyophilized powder. In certain embodiments, the lyophilized powder provided herein contains about 34% of sitaxsentan sodium, about 5.5% ascorbic acid, about 3.7% sodium phosphate dibasic heptahydrate, about 55% D-mannitol and 1.9% sodium phosphate monobasic monohydrate by total weight of the lyophilized powder. In one embodiment, the lyophilized powder has the following composition:

Sitaxsentan Sodium Lyophilized Formulation

Component	Quantity in a 10 mL vial (mg/vial)
Sitaxsentan Sodium	250.0
Sodium Phosphate Dibasic Heptahydrate	26.8
L-Ascorbic Acid	40.0
D-Mannitol	400.0
Sodium Phosphate Monobasic Monohydrate	13.9
Sodium Hydroxide or Hydrochloride Acid	QS to pH 6.8

The lyophilized formulations of sitaxsentan sodium provided herein can be administered to a patient in need thereof using standard therapeutic methods for delivering sitaxsentan sodium including, but not limited to, the methods described herein. In one embodiment, the lyophilized sitaxsentan sodium is administered by dissolving a therapeutically effective amount of the lyophilized sitaxsentan sodium provided herein in a pharmaceutically acceptable solvent to produce a pharmaceutically acceptable solution, and administering the solution (such as by intravenous injection) to the patient.

The lyophilized sitaxsentan sodium formulation provided herein can be constituted for parenteral administration to a patient using any pharmaceutically acceptable diluent. Such diluents include, but are not limited to Sterile Water for Injection, USP, Sterile Bacteriostatic Water for Injection, saline, USP (benzyl alcohol or parabens preserved). Any quantity of diluent may be used to constitute the lyophilized sitaxsentan sodium formulation such that a suitable solution for injection is prepared. Accordingly, the quantity of the diluent must be sufficient to dissolve the lyophilized

sitaxsentan sodium. In one embodiment,, 10-50 mL or 10 to 20 mL of a diluent are used to constitute the lyophilized sitaxsentan sodium formulation to yield a final concentration of, about 1-50 mg/mL, about 5-40 mg/mL, about 10-30 mg/mL or 10-25 mg/mL. In certain embodiments, the final concentration of sitaxsentan sodium in the reconstituted solution is about 25 mg/mL or about 12.5 mg/mL. The precise amount depends upon the indication treated. Such amount can be empirically determined. In some embodiments, the pH of the reconstituted solution is about 5 to about 10 or about 6 to about 8. In some embodiments, the pH of the reconstituted solution is about 5, 6, 7, 8, 9 or 10.

Constituted solutions of lyophilized sitaxsentan sodium can be administered to a patient promptly upon constitution. Alternatively, constituted solutions can be stored and used within about 1-72 hours, about 1-48 hours or about 1-24 hours. In some embodiments, the solution is used within 1 hour of preparation.

Tablet Formulations

In certain embodiments, provided herein are oral tablets containing sitaxsentan sodium. In one embodiment, the oral tablet further contains a buffer. In one embodiment, the oral tablet further contains an antioxidant. In one embodiment, the oral tablet further contains a moisture barrier coating.

In some embodiments, the tablets contain excipients, including, but not limited to an antioxidant, such as sodium ascorbate, glycine, sodium metabisulfite, ascorbyl palmitate, disodium edetate (EDTA) or a combination thereof; a binding agent, such as hydroxypropyl methylcellulose; a diluent, such as lactose monohydrate, including lactose monohydrate fast flo (intragranular) and lactose monohydrate fast flo (extragranular) and microcrystalline cellulose and a buffer, such as phosphate buffer. The tablet can further contain one or more excipients selected from a lubricant, a disintegrant and a bulking agent.

In certain embodiments, the amount of sitaxsentan sodium in the oral tablet is from about 5% to about 40% of the total weight of the composition. In certain embodiments, the amount of sitaxsentan sodium is from about 7% to about 35%, 10% to about 30%, 12% to about 32%, 15% to about 30%, 17% to about 27%, 15% to about 25% of the total weight of the composition. In certain embodiments, the amount of sitaxsentan sodium is about 5%, 7%, 9%, 10%, 12%, 15%, 17%, 20%, 22%, 25%, 27%,

30%, 35% or 40% of the total weight of the composition. In certain embodiments, the amount of sitaxsentan sodium is about 20%.

In certain embodiments, the oral tablet contains about 10 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 280 mg, 300 mg or 350 mg of sitaxsentan sodium.

In certain embodiments, the tablets contain a combination of two antioxidants, such as ascorbyl palmitate and EDTA, disodium. In certain embodiments, the amount of ascorbyl palmitate in the formulation is in a range from about 0.05% to about 3% of the total weight of the tablet. In other embodiments, the amount of ascorbyl palmitate is in a range from about 0.07% to about 1.5%, 0.1% to about 1% or 0.15% to about 0.5% of the total weight of the tablet. In certain embodiments, the amount of ascorbyl palmitate in the formulation is about 0.05%, 0.07%, 0.09%, 0.1%, 0.12%, 0.15%, 0.17%, 0.18%, 0.2%, 0.23%, 0.25%, 0.27%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.7% or 1 %. In certain embodiments, the amount of ascorbyl palmitate in the formulation is about 0.2% of the total weight of the tablet.

In certain embodiments, the amount of ascorbyl palmitate in the oral tablet is from about 0.1 mg to about 5 mg, about 0.5 mg to about 4 mg, about 0.7 mg to about 3 mg or about 1 mg to about 2 mg. In certain embodiments, the amount of ascorbyl palmitate in the oral tablet is about 0.1 mg, 0.5 mg, 0.7 mg, 1 mg, 1.3 mg, 1.5 mg, 1.7 mg, 2 mg, 2.5 mg or about 3 mg. In certain embodiments, the amount of ascorbyl palmitate in the formulation is about 1 mg.

In certain embodiments, the amount of EDTA, disodium in the formulation is in a range from about 0.05% to about 3% by weight of the total weight of the tablet. In other embodiments, the amount of EDTA, disodium is in a range from about 0.07% to about 1.5%, 0.1% to about 1% or 0.15% to about 0.5% of the total weight of the tablet. In certain embodiments, the amount of EDTA, disodium in the formulation is about 0.05%, 0.07%, 0.09%, 0.1%, 0.12%, 0.15%, 0.17%, 0.18%, 0.2%, 0.23%, 0.25%, 0.27%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.7% or 1%. In certain embodiments, the amount of EDTA, disodium in the formulation is about 0.2% of the total weight of the tablet.

In certain embodiments, the amount of EDTA, disodium in the oral tablet is from about 0.1 mg to about 5 mg, about 0.5 mg to about 4 mg, about 0.7 mg to about 3 mg or about 1 mg to about 2 mg. In certain embodiments, the amount of EDTA, disodium in

the oral tablet is about 0.1 mg, 0.5 mg, 0.7 mg, 1 mg, 1.3 mg, 1.5 mg, 1.7 mg, 2 mg, 2.5 mg or about 3 mg. In certain embodiments, the amount of EDTA, disodium in the oral tablet is about 1 mg.

In certain embodiments, the tablets contain a combination of diluents, such as microcrystalline cellulose (AVICEL PH 102), lactose monohydrate fast flo (intragranular) and lactose monohydrate fast flo (extragranular). In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) in the oral tablet is from about 5% to about 30% of the total weight of the composition. In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) is from about 7% to about 25%, from about 10% to about 20% or from about 13% to about 20% of the total weight of the tablet. In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) is about 5%, 7%, 10%, 13%, 14%, 15%, 15.5%, 16%, 16.1%, 16.2%, 16.3%, 16.4%, 16.5%, 16.6%, 16.7%, 16.8%, 16.9%, 17%, 17.5%, 18%, 18.5%, 19%, 20%, 25% or 30% of the total weight of the tablet. In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) is about 16.9% of the total weight of the tablet.

In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) is from about 40 mg to about 100 mg, from about 45 mg to about 95 mg or from about 50 mg to about 90 mg. In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) is about 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 81 mg, 82 mg, 83 mg, 83.5 mg, 84 mg, 84.1 mg, 84.2 mg, 84.3 mg, 84.4 mg, 84.5 mg, 84.6 mg, 84.7 mg, 85 mg, 85.5 mg, 90 mg, 90.5 mg or 100 mg. In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) is about 84.3 mg.

In certain embodiments, the amount of lactose monohydrate fast flo (extragranular) is from about 7% to about 25%, from about 10% to about 20% or from about 13% to about 20% of the total weight of the tablet. In certain embodiments, the amount of lactose monohydrate fast flo (extragranular) is about 5%, 7%, 10%, 13%, 14%, 15%, 15.5%, 16%, 16.1%, 16.2%, 16.3%, 16.4%, 16.5%, 16.6%, 16.7%, 16.8%, 16.9%, 17%, 17.5%, 18%, 18.5%, 19%, 20%, 25% or 30% of the total weight of the tablet. In certain embodiments, the amount of lactose monohydrate fast flo (extragranular) is about 16.4% of the total weight of the tablet. In certain embodiments,

the amount of lactose monohydrate fast flo (extragranular) in the oral tablet is from about 40 mg to about 100 mg, from about 45 mg to about 95 mg or from about 50 mg to about 90 mg. In certain embodiments, the amount of lactose monohydrate fast flo (extragranular) is about 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 81 mg, 81.3 mg, 81.5 mg, 81.8 mg, 82 mg, 82.3 mg, 82.5 mg, 82.7 mg, 83 mg, 83.5 mg, 84 mg, 85 mg, 85.5 mg, 90 mg, 90.5 mg or 100 mg. In certain embodiments, the amount of lactose monohydrate fast flo (intragranular) is about 82 mg.

In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) in the oral tablet is from about 10% to about 50% of the total weight of the composition. In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) is from about 15% to about 45%, from about 20% to about 43% or from about 25% to about 40% of the total weight of the tablet. In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) is about 15%, 17%, 20%, 23%, 25%, 27%, 30%, 32%, 34%, 35%, 37%, 40%, 42%, 45% or 50% of the total weight of the tablet. In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) is about 35% of the total weight of the tablet.

In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) in the oral tablet is from about 130 mg to about 300 mg. In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) is from about 140 mg to about 275 mg or about 150 mg to about 250 mg. In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) is about 150 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg or 200 mg. In certain embodiments, the amount of microcrystalline cellulose (Avicel PH 102) in the oral tablet is about 175 mg.

In certain embodiments, the binding agent is hydroxypropyl methylcellulose (E-5P). In certain embodiments, the amount of hydroxypropyl methylcellulose (E-5P) in the tablet is from about 0.5% to about 20% of the total weight of the composition. In certain embodiments, the amount of hydroxypropyl methylcellulose (E-5P) is from about 1% to about 15%, from about 2% to about 10% or from about 3% to about 8% of the total weight of the tablet. In certain embodiments, the amount of hydroxypropyl methylcellulose (E-5P) is about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9% or 10% of the total weight of the tablet. In certain embodiments, the amount of hydroxypropyl methylcellulose (E-5P) is about 5% of the total weight of the tablet.

In certain embodiments, the amount of hydroxypropyl methylcellulose (E-5P) in the tablet is from about 5 mg to about 50 mg, about 10 mg to about 40 mg or about 15 mg to about 30 mg. In certain embodiments, the amount of hydroxypropyl methylcellulose (E-5P) in the tablet is about 10 mg, 15 mg, 20 mg, 22 mg, 25 mg, 27 mg, 30 mg, 35 mg or about 40 mg. In certain embodiments, the amount of hydroxypropyl methylcellulose (E-5P) in the tablet is about 25 mg.

The formulations of sitaxsentan sodium provided herein are stable at neutral pH. In certain embodiments, buffer agent mixture, such as sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous is used to improve drug stability in the tablets. In certain embodiments, the amount of sodium phosphate, monobasic monohydrate ranges from about 0.05% to about 3% by weight of the total weight of the tablet. In other embodiments, the amount of sodium phosphate, monobasic monohydrate is in a range from about 0.07% to about 1.5%, 0.1% to about 1% or 0.15% to about 0.5% of the total weight of the tablet. In certain embodiments, the amount of sodium phosphate, monobasic monohydrate in the formulation is about 0.05%, 0.07%, 0.09%, 0.1%, 0.12%, 0.15%, 0.17%, 0.18%, 0.2%, 0.23%, 0.25%, 0.27%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.7% or 1.% of the total weight of the tablet. In certain embodiments, the amount of sodium phosphate, monobasic monohydrate in the formulation is about 0.1% of the total weight of the tablet.

In certain embodiments, the amount of sodium phosphate, monobasic monohydrate in the oral tablet is from about 0.1 mg to about 3 mg, about 0.2 mg to about 2.5 mg, about 0.5 mg to about 2 mg or about 0.6 mg to about 1 mg. In certain embodiments, the amount of sodium phosphate, monobasic monohydrate in the oral tablet is about 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg or about 1 mg. In certain embodiments, the amount of sodium phosphate, monobasic monohydrate in the oral tablet is about 0.6 mg.

In certain embodiments, the amount of sodium phosphate, dibasic anhydrous ranges from about 0.05% to about 3% by weight of the total weight of the tablet. In other embodiments, the amount of sodium phosphate dibasic is in a range from about 0.07% to about 1.5%, 0.1% to about 1% or 0.15% to about 0.5% of the total weight of the tablet. In certain embodiments, the amount of sodium phosphate dibasic in the formulation is about 0.05%, 0.07%, 0.09%, 0.1%, 0.12%, 0.15%, 0.17%, 0.18%, 0.2%,

0.23%, 0.25%, 0.27%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.7% or 1.% of the total weight of the tablet. In certain embodiments, the amount of sodium phosphate dibasic in the formulation is about 0.2% of the total weight of the tablet.

In certain embodiments, the amount of sodium phosphate, dibasic anhydrous in the oral tablet is from about 0.1 mg to about 3.5 mg, about 0.5 mg to about 2.5 mg, or about 0.7 mg to about 2 mg. In certain embodiments, the amount of sodium phosphate, dibasic anhydrous in the oral tablet is about 0.1 mg, 0.3 mg, 0.5 mg, 0.7 mg, 0.9 mg, 1 mg, 1.1 mg, 1.3 mg, 1.5 mg, 1.7 mg or 2 mg. In certain embodiments, the amount of sodium phosphate, dibasic anhydrous in the oral tablet is about 1.1 mg.

In certain embodiments, the tablet contains disintegrants, such as sodium starch glycoloate (intragranular) and sodium starch glycoloate (extragranular). In certain embodiments, the amount of sodium starch glycoloate (intragranular) in the tablet is from about 0.1% to about 10% of the total weight of the composition. In certain embodiments, the amount of sodium starch glycoloate (intragranular) is from about 0.5% to about 8%, from about 1% to about 5% or from about 2% to about 4% of the total weight of the tablet. In certain embodiments, the amount of sodium starch glycoloate (intragranular) is about 0.5%, 1%, 1.5%, 1.7%, 2%, 2.3%, 2.5%, 2.7%, 3%, 3.5%, 4% or 5% of the total weight of the tablet. In certain embodiments, the amount of Sodium Starch Glycoloate (intragranular) is about 2.5% of the total weight of the tablet. In certain embodiments, the amount of sodium starch glycoloate (intragranular) is from about 30 mg to about 5 mg, from about 20 mg to about 10 mg, from about 15 to about 10 mg. In certain embodiments, the amount of sodium starch glycoloate (intragranular) is about 5 mg, 7 mg, 10 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 15 mg or 20 mg. In certain embodiments, the amount of sodium starch glycoloate (intragranular) is about 12.5 mg.

In certain embodiments, the amount of sodium starch glycoloate (extragranular) in the tablet is from about 0.1% to about 10% of the total weight of the composition. In certain embodiments, the amount of sodium starch glycoloate (extragranular) is from about 0.5% to about 8%, from about 1% to about 5% or from about 2% to about 4% of the total weight of the tablet. In certain embodiments, the amount of sodium starch glycoloate (extragranular) is about 0.5%, 1%, 1.5%, 1.7%, 2%, 2.3%, 2.5%, 2.7%, 3%, 3.5%, 4% or 5% of the total weight of the tablet. In certain embodiments, the amount of

sodium starch glycoloate (extragranular) is about 2.5% of the total weight of the tablet. In certain embodiments, the amount of sodium starch glycoloate (extragranular) is from about 30 mg to about 5 mg, from about 20 mg to about 10 mg or from about 15 to about 10 mg. In certain embodiments, the amount of sodium starch glycoloate (extragranular) is about 5 mg, 7 mg, 10 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 15 mg or 20 mg. In certain embodiments, the amount of sodium starch glycoloate (extragranular) is about 12.5 mg.

In certain embodiments, the tablet contains a lubricant, such as magnesium stearate. In certain embodiments, the amount of magnesium stearate in the tablet is from about 0.1% to about 8% of the total weight of the composition. In certain embodiments, the amount of magnesium stearate is from about 0.5% to about 6%, from about 0.7% to about 5% or from about 1% to about 4% of the total weight of the tablet. In certain embodiments, the amount of magnesium stearate is about 0.5%, 0.7%, 1%, 1.2%, 1.5%, 1.7%, 2%, 2.5% or 3% of the total weight of the tablet. In certain embodiments, the amount of magnesium stearate is about 2.5% of the total weight of the tablet. In certain embodiments, the amount of magnesium stearate in the tablet is from about 15 mg to about 1 mg. In certain embodiments, the amount of magnesium stearate is from about 10 mg to about 3 mg or from about 7 mg to about 5 mg. In certain embodiments, the amount of magnesium stearate is about 3 mg, 4 mg, 4.5 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg or 10 mg. In certain embodiments, the amount of magnesium stearate is about 5 mg.

In one embodiment, the tablet formulations provided herein contain a moisture barrier coating. Suitable coating materials are known in the art and include, but are not limited to coating agents either of cellulose origin such as hydroxypropylmethylcellulose (Sepifilm®, Pharmacoat), or of polyvinyl origin of Sepifilm® ECL type, or of saccharose origin such as the sugar for sugar-coating of Sepisperse DR, AS, AP OR K (coloured) type, such as Sepisperse Dry 3202 Yellow, Blue Opadry, Eudragit EPO and Opadry AMB. Without being bound by any particular theory, it is believed that the coating serves as a moisture barrier to hinder oxidation of sitaxsentan sodium. In certain embodiments, the coating materials are Sepifilm® LP014/Sepisperse Dry 3202 Yellow (Sepifilm®/Sepisperse) (3/2 wt/wt) at from about 1 to about 7% or about 4% tablet weight gain. In certain embodiments, the coating material is Sepifilm® LP014/Sepisperse Dry 3202 Yellow (Sepifilm®/Sepisperse). In certain embodiments,

the Sepifilm®/Sepisperse ratio is 1:2, 1:1 or 3:2 wt/wt. In certain embodiments, the Sepifilm®/Sepisperse coating is at about 1%, 2%, 3%, 4%, 5%, 6% or 7% tablet weight gain. In certain embodiments, the Sepifilm®/Sepisperse coating is at about 1.6% tablet weight gain. In certain embodiments, the Sepisperse Dry 3202 (yellow) is at about 0.5%, 0.8%, 1%, 1.3%, 1.6%, 2%, 2.4%, 2.5%, 3% or 4% tablet weight gain. In certain embodiments, the Sepisperse Dry 3202 (yellow) is at about 2.4% tablet weight gain. In certain embodiments, the Sepisperse Dry 3202 (yellow) is at about 1 mg, 3 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 13 mg 15 mg or 20 mg per tablet. In certain embodiments, the Sepisperse Dry 3202 (yellow) is at about 8 mg per tablet. In certain embodiments, the Sepifilm® LP 014 is at about 0.5%, 1%, 1.5%, 2%, 2.2%, 2.4%, 2.6%, 3%, 3.5% or 4% tablet weight gain. In certain embodiments, the Sepifilm® LP 014 is at about 2.4% tablet weight gain. In certain embodiments, the Sepifilm® LP 014 is at about 5 mg, 7 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 15 mg, 17 mg or 20 mg per tablet. In certain embodiments, the Sepifilm® LP 014 coating is at about 12 mg per tablet.

In certain embodiments, the tablet contains sitaxsentan sodium, microcrystalline cellulose, lactose monohydrate fast flo (intragranular), lactose monohydrate fast flo (extragranular), hydroxypropyl methylcellulose E-5P, ascorbyl palmitate, disodium EDTA, sodium phosphate monobasic, monohydrate, sodium phosphate dibasic, anhydrous, Sodium Starch Glycoloate (intragranular), Sodium Starch Glycoloate (extragranular), magnesium stearate and a coating of Sepifilm® LP014/Sepisperse Dry 3202 Yellow.

In certain embodiments, the tablet contains about 20% sitaxsentan sodium, about 35% microcrystalline cellulose, about 16.9% lactose monohydrate fast flo (intragranular), about 16.4% lactose monohydrate fast flo (extragranular), about 5.0% hydroxypropyl methylcellulose E-5P, about 0.2% ascorbyl palmitate, about 0.2% disodium (EDTA), about 0.1% sodium phosphate monobasic, monohydrate, about 0.2% sodium phosphate dibasic, anhydrous, about 2.5 % Sodium Starch Glycoloate (extragranular), about 2.5 % Sodium Starch Glycoloate (intragranular) and about 1 % magnesium stearate. The tablet further contains a coating of Sepifilm® LP014 at about 2.4 % weight gain and Sepisperse Dry 3202 Yellow at about 1.6% weight gain.

In certain embodiments, the oral tablet provided herein is a 500 mg tablet that contains about 100 mg sitaxsentan sodium, about 1.0 mg ascorbyl palmitate, about 1.0 mg disodium edetate (EDTA), about 25 mg hydroxypropyl methylcellulose E-5P, about 84.3 lactose monohydrate fast flo (intragranular), about 82 mg lactose monohydrate fast flo (extragranular), about 175 mg microcrystalline cellulose, about 0.6 mg sodium phosphate monobasic, monohydrate, about 1.1 mg sodium phosphate dibasic, anhydrous, about 12.5 mg Sodium Starch Glycoloate (extragranular), about 12.5 mg Sodium Starch Glycoloate (intragranular), about 5 mg magnesium stearate, non-bovine and about 192.5 mg purified water. The tablet further contains a coating of Sepifilm® LP014 at about 12 mg and Sepisperse Dry 3202 Yellow at about 8 mg.

D. Dosages

In human therapeutics, the physician will determine the dosage regimen that is most appropriate according to a preventive or curative treatment and according to the age, weight, stage of the disease and other factors specific to the subject to be treated. In certain embodiments, dose rates of sitaxsentan sodium are from about 1 to about 350 mg per day for an adult, from about 1 to about 300 mg per day, from about 5 to about 250 mg per day, from about 5 to about 250 mg per day or from about 10 to 50 mg per day for an adult. Dose rates of from about 50 to about 300 mg per day are also contemplated herein. In certain embodiments, doses are about 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 125 mg, 150 mg, 175 mg or 200 mg per day per adult.

The amount of sitaxsentan sodium in the formulations provided herein which will be effective in the prevention or treatment of a disorder or one or more symptoms thereof will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (e.g., therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject.

Exemplary doses of a formulation include milligram or microgram amounts of the active compound per kilogram of subject or sample weight (e.g., from about 1 micrograms per kilogram to about 3 milligrams per kilogram, from about 10 micrograms

per kilogram to about 3 milligrams per kilogram, from about 100 micrograms per kilogram to about 3 milligrams per kilogram, or from about 100 microgram per kilogram to about 2 milligrams per kilogram). In certain embodiments, the amount of sitaxsentan sodium administered is from about 0.01 to about 3 mg/kg for a subject in need thereof. In certain embodiments, the amount of sitaxsentan sodium administered is about 0.01, 0.05, 0.1, 0.2, 0.4, 0.8, 1.5, 2 or 3 mg/kg of a subject. In the certain embodiments, the administration of sitaxsentan sodium is by intravenous injection.

It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the composition provided herein are also encompassed by the above described dosage amounts and dose frequency schedules. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. For example, the dosage administered to the subject may be increased to improve the prophylactic or therapeutic effect of the composition or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

In another embodiment, the dosage of the formulation provided herein is administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject in a unit dose contain sitaxsentan sodium from about 1 mg to 300 mg, 50 mg to 250 mg or 75 mg to 200 mg.

In certain embodiments, administration of the same formulation provided herein may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

E. Methods of preparation

Sitaxsentan sodium can be prepared by methods known in the art. An exemplary methods for the preparation are described in Example 1. (Also see, U.S. Patent Nos.

5,783,705, 5,962,490 and 6,248,767; and Wu *et al.*, *J. Med. Chem.* 1997, 40, 1690-1697).

The lyophilized and tablet formulations of sitaxsentan sodium can be prepared by methods known in the art and as described herein. In one embodiment, the process for making lyophilized formulation involves lyophilizing a solution of sitaxsentan sodium using a primary drying stage of duration from about 2 to 10 hours, or about 4 hours at from about -20°C to about -60°C, or at about -40°C. The process further involves a secondary drying stage of duration for about 30 hours to about 70 hours, or about 50 hours at from about -30°C to about -5°C. An exemplary process for producing the lyophilized formulations is described in Examples section.

F. Evaluation of the Activity

Standard physiological, pharmacological and biochemical procedures are available and are known to one of skill in the art (see, for example 6,432,994; 6,683,103; 6,686,382; 6,248,767; 6,852,745; 5,783,705; 5,962,490; 5,594,021; 5,571821; 5,591,761; 5,514,691. 5,352,800, 5,334,598, 5,352,659, 5,248,807, 5,240,910, 5,198,548, 5,187,195, 5,082,838, 6,953,780, 6,946,481, 6,852,745, 6,835,741, 6,673,824, 6,670,367 and 6,670,362) to test the efficacy of sitaxsentan sodium formulations in the methods provided herein.

G. Methods of Treatment

Methods for the treatment of endothelin-mediated disorders by administering the lyophilized formulations provided herein. In certain embodiments, the disorder is selected from hypertension, cardiovascular disease, asthma, pulmonary hypertension, inflammatory diseases, ophthalmologic disease, menstrual disorders, obstetric conditions, wounds, gastroenteric disease, renal failure, immunosuppressant-mediated renal vasoconstriction, erythropoietin-mediated vasoconstriction, endotoxin shock, anaphylactic shock and hemorrhagic shock. In one embodiment, the disorder is pulmonary hypertension.

H. Combination Therapy

Sitaxsentan sodium formulations provided herein can be employed alone or in combination with other suitable therapeutic agents useful in the treatment of the diseases treated by these formulations. For example, the formulations can be administered in

combination with other compounds known to modulate the activity of endothelin receptor.

Further, the formulations provided herein can be employed in combination with endothelin antagonists known in the art and include, but are not limited to a fermentation product of Streptomyces misakiensis, designated BE-18257B which is a cyclic pentapeptide, cyclo(D-Glu-L-Ala-allo-D-Ile-L-Leu-D-Trp); cyclic pentapeptides related to BE-18257B, such as cyclo(D-Asp-Pro-D-Val-Leu-D-Trp) (BQ-123) (*see,* U.S. Pat. No. 5,114,918 to Ishikawa *et al.; see,* also, EP A1 0 436 189 to BANYU PHARMACEUTICAL CO., LTD (Oct. 7, 1991)); and other peptide and non-peptidic ETA antagonists have been identified in, for example, U.S. Pat. Nos. 6,432,994; 6,683,103; 6,686,382; 6,248,767; 6,852,745; 5,783,705; 5,962,490; 5,594,021; 5,571821; 5,591,761; 5,514,691; 5,352,800; 5,334,598; 5,352,659; 5,248,807; 5,240,910; 5,198,548; 5,187,195; 5,082,838; 6,953,780; 6,946,481; 6,852,745; 6,835,741; 6,673,824; 6,670,367; and 6,670,362. These include other cyclic pentapeptides, acyltripeptides, hexapeptide analogs, certain anthraquinone derivatives, indanecarboxylic acids, certain N-pyriminylbenzenesulfonamides, certain benzenesulfonamides, and certain naphthalenesulfonamides (Nakajima *et al.* (1991) *J. Antibiot.* 44:1348-1356; Miyata *et al.* (1992) *J. Antibiot.* 45:74-8; Ishikawa *et al.* (1992) *J .Med. Chem.* 35:2139-2142; U.S. Pat. No. 5,114,918 to Ishikawa *et al.*; EP A1 0 569 193; EP A1 0 558 258; EP A1 0 436 189 to BANYU PHARMACEUTICAL CO., LTD (Oct. 7, 1991); Canadian Patent Application 2,067,288; Canadian Patent Application 2,071,193; U.S. Pat. No. 5,208,243; U.S. Pat. No. 5,270,313; U.S. Pat. No. 5,612,359, U.S. Pat. No. 5,514,696, U.S. Pat. No. 5,378,715; Cody *et al.* (1993) *Med. Chem. Res.* 3:154-162; Miyata *et al.* (1992) *J. Antibiot* 45:1041-1046; Miyata *et al.* (1992) *J. Antibiot* 45:1029-1040, Fujimoto *et al.* (1992) *FEBS Lett.* 305:41-44; Oshashi *et al.* (1002) *J. Antibiot* 45:1684-1685; EP A1 0 496 452; Clozel *et al.* (1993) *Nature* 365:759-761; International Patent Application WO93/08799; Nishikibe *et al.* (1993) *Life Sci.* 52:717-724; and Benigni *et al.* (1993) *Kidney Int.* 44:440-444). Numerous sulfonamides that are endothelin peptide antagonists are also described in U.S. Pat. Nos. 5,464,853; 5,594,021; 5,591,761; 5,571,821; 5,514,691; 5,464,853; International PCT application No.96/31492; and International PCT application No. WO 97/27979.

Further endothelin antagonists described in the following documents, incorporated herein by reference in their entirety, are exemplary of those contemplated for use in combination with the formulations provided herein: U.S. Pat. No. 5,420,123; U.S. Pat. No. 5,965,732; U.S. Pat. No. 6,080,774; U.S. Pat. No. 5,780,473; U.S. Pat. No. 5,543,521; WO 96/06095; WO 95/08550; WO 95/26716; WO 96/11914; WO 95/26360; EP 601386; EP 633259; U.S. Pat. No. 5,292,740; EP 510526; EP 526708; WO 93/25580; WO 93/23404; WO 96/04905; WO 94/21259; GB 2276383; WO 95/03044; EP 617001; WO 95/03295; GB 2275926; WO 95/08989; GB 2266890; EP 496452; WO 94/21590; WO 94/21259; GB 2277446; WO 95/13262; WO 96/12706; WO 94/24084; WO 94/25013; U.S. Pat. No. 5,571,821; WO 95/04534; WO 95/04530; WO 94/02474; WO 94/14434; WO 96/07653; WO 93/08799; WO 95/05376; WO 95/12611; DE 4341663; WO 95/15963; WO 95/15944; EP 658548; EP 555537; WO 95/05374; WO 95/05372; U.S. Pat. No. 5,389,620; EP 628569; JP 6256261; WO 94/03483; EP 552417; WO 93/21219; EP 436189; WO 96/11927; JP 6122625; JP 7330622; WO 96/23773; WO 96/33170; WO 96/15109; WO 96/33190; U.S. Pat. No. 5,541,186; WO 96/19459; WO 96/19455; EP 713875; WO 95/26360; WO 96/20177; JP 7133254; WO 96/08486; WO 96/09818; WO 96/08487; WO 96/04905; EP 733626; WO 96/22978; WO 96/08483; JP 8059635; JP 7316188; WO 95/33748; WO 96/30358; U.S. Pat. No. 5,559,105; WO 95/35107; JP 7258098; U.S. Pat. No. 5,482,960; EP 682016; GB 2295616; WO 95/26957; WO 95/33752; EP 743307; and WO 96/31492; such as the following compounds described in the recited documents: BQ-123 (Ihara, M., *et al.*, "Biological Profiles of Highly Potent Novel Endothelin Antagonists Selective for the ET_A Receptor", *Life Sciences*, Vol. 50(4), pp. 247-255 (1992)); PD 156707 (Reynolds, E., *et al.*, "Pharmacological Characterization of PD 156707, an Orally Active ET_A Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics,* Vol. 273(3), pp. 1410-1417 (1995)); L-754,142 (Williams, D. L., *et al.*, "Pharmacology of L-754,142, a Highly Potent, Orally Active, Nonpeptidyl Endothelin Antagonist", *The Journal of Pharmacology and Experimental Therapeutics,* Vol. 275(3), pp. 1518-1526 (1995)); SB 209670 (Ohlstein, E. H., *et al.*, "SB 209670, a rationally designed potent nonpeptide endothelin receptor antagonist", *Proc. Natl. Acad. Sci. USA,* Vol. 91, pp. 8052-8056 (1994)); SB 217242 (Ohlstein, E. H., *et al.*, "Nonpeptide Endothelin Receptor Antagonists. VI:Pharmacological Characterization of SB 217242, A Potent and Highly

Bioavailable Endothelin Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics,* Vol. 276(2), pp. 609-615 (1996)); A-127722 (Opgenorth, T. J., *et al.*, "Pharmacological Characterization of A-127722: An Orally Active and Highly Potent E.sub.TA -Selective Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics,* Vol. 276(2), pp.473-481 (1996)); TAK-044 (Masuda, Y., *et al.*, "Receptor Binding and Antagonist Properties of a Novel Endothelin Receptor Antagonist, TAK-044 {Cyclo [D-α-Aspartyl-3-[(4-Phenylpiperazin-1-yl)Carbonyl]-L-Alanyl-L- α -Aspartyl-D-2-(2-Thienyl)Glycyl-L-Leucyl-D-Tryptophyl]Disodium Salt}, in Human Endothelin$_A$ and Endothelin$_B$ Receptors", *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 279(2), pp. 675-685 (1996)); bosentan (Ro 47-0203, Clozel, M., *et al.*, "Pharmacological Characterization of Bosentan, A New Potent Orally Active Nonpeptide Endothelin Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics,* Vol. 270(1), pp. 228-235 (1994)).

The formulations provided herein can also be administered in combination with other classes of compounds. Exemplary classes of compounds for combinations herein include endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; thromboxane receptor antagonists such as ifetroban; potassium channel openers; thrombin inhibitors (e.g., hirudin and the like); growth factor inhibitors such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; anti-platelet agents such as GPIIb/IIIa blockers (e.g., abdximab, eptifibatide, and tirofiban). P2Y(AC) antagonists (e.g., clopidogrel, ticlopidine and CS-747), and aspirin; anticoagulants such as warfarin, low molecular weight heparins such as enoxaparin, Factor VIIa Inhibitors, and Factor Xa Inhibitors, renin inhibitors; angiotensin converting enzyme (ACE) inhibitors such as captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, lisinopril and salts of such compounds; neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) such as omapatrilat and gemopatrilat; HMG CoA reductase Inhibitors such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (also known as rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants such as questran; niacin; anti-atherosclerotic agents such as ACAT inhibitors; MTP Inhibitors: calcium channel blockers such as amlodipine besylate; potassium channel activators; alpha-adrenergic

agents, beta-adrenergic agents such as carvedilol and metoprolol; antiarrhythmic agents; diuretics, such as chlorothlazide, hydrochiorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichioromethiazide, polythiazide or benzothlazide as well as ethacrynic acid, tricrynafen, chlorthalidone, furosenilde, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds; thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase and anisoylated plasminogen streptokinase activator complex (APSAC); anti-diabetic agents such as biguanides (e.g. metformin), glucosidase inhibitors (e.g., acarbose), insulins, meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, and glipizide), thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), and PPAR-gamma agonists; mineralocorticoid receptor antagonists such as spironolactone and eplerenone; growth hormone secretagogues; aP2 inhibitors; non-steroidal antiinflammatory drugs (NSAIDS) such as aspirin and ibuprofen; phosphodiesterase inhibitors such as PDE III inhibitors (e.g., cilostazol) and PDE V inhibitors (e.g., sildenafil, vardenafil, tadalafil); protein tyrosine kinase inhibitors; antiinflammatories; antiproliferatives such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate and mofetil; chemotherapeutic agents; immunosuppressants; anticancer agents and cytotoxic agents (e.g., alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes): antimetabolites such as folate antagonists, purine analogues, and pyrridine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids (e.g., cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone anatagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives: microtubule-stablizing agents such as pacitaxel (Taxol®), docetaxel (Taxotere®), and epothilones A-F or their analogs or derivatives; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors: prenyl-protein transferase inhibitors: and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin, satraplatin, and carboplatin); cyclosporins; steroids such as prednisone or dexamethasone; gold

compounds; cytotoxic drugs such as azathiprine and cyclophosphamide: TNF-alpha inhibitors such as tenidap; anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel) rapamycin (sirolimus or Rapamune), leflunimide (Arava); and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx).

I. Article of Manufacture

Also provided are articles of manufacture, containing packaging material and a formulation of sitaxsentan sodium provided herein within the packaging material, and a label that indicates that the formulation is used for treating an endothelin-mediated disorder.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, *e.g.*, U.S. Patent Nos. 5,323,907; 5,052,558; and 5,033,352. Examples of pharmaceutical packaging materials include, but are not limited to, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

It is understood that the foregoing detailed description and accompanying examples are merely illustrative, and are not to be taken as limitations upon the scope of the subject matter. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use provided herein, may be made without departing from the spirit and scope thereof. U.S. patents and publications referenced herein are incorporated by reference.

EXAMPLES

Example 1: Preparation of 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole, sodium salt or N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]-thiophene-3-sulfonamide, sodium salt or N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methylphenylacetyl]-thiophene-3-sulfonamide, sodium salt.

A. Preparation of (4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole

1. Preparation of 5-chloromethyl-6-methylbenzo[d][1,3]dioxole

To a mixture of methylene chloride (130 L), concentrated HCl (130 L), and tetrabuylammonium bromide (1.61 Kg) was added 5-methylbenzo[d][1,3]dioxole (10 Kg) followed by the slow addition of formaldehyde (14 L, 37 wt% in water). The mixture was stirred overnight. The organic layer was separated, dried with magnesium sulfate and concentrated to an oil. Hexane (180 L) was added and the mixture heated to boiling. The hot hexane solution was decanted from a heavy oily residue and evaporated to give almost pure 5-chloromethyl-6-methylbenzo[d][1,3]dioxole as a white solid. Recrystallization from hexane (50 L) gave 5-chloromethyl-6-methylbenzo[d][1,3]dioxole (80% recovery after recrystallization).

2. Formation of (4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl) acetyl)-3-thienylsulfonamido)isoxazole

A portion of a solution of 5-chloromethyl-6-methylbenzo[d][1,3]di-oxole (16.8 g, 0.09 mol) in tetrahydrofuran (THF)(120 mL) was added to a well stirred slurry of magnesium powder, (3.3 g, 0.136 g-atom, Alfa, or Johnson-Mathey, -20 +100 mesh) in THF (120 mL) at room temperature. The resulting reaction admixture was warmed to about 40-45 °C for about 2-3 min, causing the reaction to start. Once the magnesium was activated by the heating, and the reaction begun, the mixture was cooled and maintained at a temperature below about 8 °C. The magnesium can be activated with dibromoethane in place of heat.

A flask containing the reaction mixture was cooled and the remaining solution of 5-chloromethlybenzo[d][1,3]dioxole added dropwise during 1.5 hours while maintaining an internal temperature below 8 °C. Temperature control is important: if the Grignard is generated and kept below 8 °C, no Wurtz coupling takes place. Longer times at higher temperatures promote the Wurtz coupling pathway. Wurtz coupling can be avoided by

using high quality Mg and by keeping the temperature of the Grignard below about 8 °C and stirring vigorously. The reaction works fine at -20 °C, so any temperature below 8 °C is acceptable at which the Grignard will form. The color of the reaction mixture turns greenish.

The reaction mixture was stirred for an additional 5 min at 0 °C, while N^2-methoxy-N^2-methyl-3-(4-chloro-3-methyl-5-isoazolylsulfamoyl)-2-thiophenecarboxamide (6.6 g, 0.018 mol) in anhydrous THF (90 mL) was charged into the addition funnel. The reaction mixture was degassed two times then the solution of N^2-methoxy-N^2-methyl-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide was added at 0 °C over 5 min. TLC of the reaction mixture (Silica, 12% MeOH/CH_2Cl_2) taken immediately after the addition shows no N^2-methoxy-N^2-methyl-3-(4-chloro-3-methyl-5-isoxazolysulfamoyl)-2-thiophenecarboxamide.

The reaction mixture was transferred into a flask containing 1N HCl (400 mL, 0.4 mol HCl, ice-bath stirred), and the mixture stirred for 2 to 4 min, transferred into a separatory funnel and diluted with ethyl acetate (300 mL). The layers were separated after shaking. The water layer was extracted with additional ethyl acetate (150 mL) and the combined organics washed with half-brine. Following separation, THF was removed by drying the organic layer over sodium sulfate and concentrating under reduced pressure at about 39 °C.

B. Preparation of 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5 yl)acetyl)-3-thienylsulfonamido)isoxazole, sodium salt

The product from part A was then re-dissolved in ethyl acetate and washed with saturated $NaHCO_3$ (5 x 50 mL) until the washings became colorless. The solution was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a semicrystalline yellow residue. 100 mL of CH_2Cl_2 was added to the solution and the mixture stirred under nitrogen for from 5 to 10 minutes until a fine crystalline product was formed. Ether (150 mL) was added and the mixture stirred from an appropriate time (e.g., 10 min). The product was isolated by filtration, washed with a mixture of CH_2Cl_2/ether (1:2) (30 mL) then with ether (30 mL) and dried under reduced pressure. When prepared in accordance with the specific embodiments set forth above, the title product was produced in quantity of 7.3 g with a purity of around 85% (HPLC, RP, 40%

acetonitrile/water, 0.1% TFA neutralized with ammonia to pH2.5, isocratic conditions, 1 mL/min).

The salt product from above was dissolved in water (600 mL) at 10 °C, the solution stirred for a short period of time (e.g., 3 min) and then filtered through a layer of paper filters (e.g., 3 filters) with suction. In some cases, the large amount of impurities that are not soluble in water (10% or higher) slows down the filtration process extremely. This problem can be avoided by using a larger size filter during the filtration. Usually there is no problem with filtration if the purity of the crude salt is 90% or higher.

The greenish slightly turbid solution obtained from filtration was cooled in an ice bath and acidified to a pH of 2 using an acid such as 4N HCl. When the pH of the solution was 2, the product precipitates as a milky, non-filterable material. Slow dropwise addition of extra 4N HCl causes the product to form a fine, easily filterable precipitate. The pale yellow precipitate was filtered off, washed with water until neutral and pressed on the filter to get rid of excess of water). The obtained free acid was typically 95% pure as determined by HPLC.

The free acid form of the product was dissolved in ethyl acetate (about 100 mL), washed with brine (30 mL) to remove water. The dehydrated solution was shaken with cold saturated $NaHCO_3$ solution (2 x 30 mL), then with brine again, dried over Na_2SO_4 and concentrated *in vacuo* (bath temperature lower than 40 °C) to give a very bright yellow foam. After complete removal of the ethyl acetate from this product, CH_2Cl_2 (100 mL) was added and the mixture stirred for 5 to 10 min until the product became crystalline. Ether (150 mL) was added and stirring continued for 10 min longer. The formed solid was isolated by filtration, washed with a mixture of CH_2Cl_2/ether (1:2)(30mL) then with ether (30 mL) and dried under reduced pressure. When purified in this manner, 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsufonamido)isoxazole, sodium salt was obtained in high yield (5.7g, 68%) with good purity (98.2% pure by HPLC). The product can also be further purified by recrystallization from EtOH/methyl *t*-butylether (MTBE) after the above procedure if the initial purity is sufficiently high.

C. N-(4-Chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methyl]-phenylacetyl-3-thiophenesulfonamide,sodium hydrogen phosphate salt also designated 4-Chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole, sodium hydrogen phosphate salt

To a solid mixture of n-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methyl]phenylacetyl-3-thiophenesulfonamide (1.1492 g, 2.5263 mmol) and sodium phosphate dibasic (0.3486 g, 2.5263 mmol) was added de-ionized water (25 ml) and acetonitrile (25 ml). The resulting mixture was well shaken and warmed at 50 °c to obtain a clear solution, which was filtered. The filtrate was frozen at -78 °c and lyophilized to give the salt as a yellow powder (≈1.50 g).

Exemplary Formulations of sitaxsentan sodium:

The following examples provide exemplary lyophilized and tablet formulations of sitaxsentan sodium and their stability studies.

A. Lyophilized Formulations

Example 2. A Solution Stability Study To Determine The Effectiveness Of Various Antioxidants

Stability of eight experimental antioxidant formulations was compared with the previously known formulation (*See*, WO 98/49162) of sitaxsentan sodium as below. The sitaxsentan sodium was present at 25 mg/mL in each of the following formulations:

I: Monothioglycerol at 10 mg/mL and disodium EDTA at 2 mg/mL in 20 mM citrate buffer at pH 6 + 40 mg/mL dextrose

II: Monothioglycerol at 10 mg/mL in 20 mM citrate buffer at pH 6 + 40 mg/mL dextrose

III: Ascorbic acid at 2 mg/mL, sodium bisulfite at 6.6 mg/mL and sodium sulfite at 2 mg/mL, 20 mM citrate pH 6 + 40 mg/mL dextrose

IV: Sodium sulfite at 2 mg/mL in 20 mM phosphate at pH 8 + 40 mg/mL dextrose

V: EDTA disodium at 2 mg/mL in 20 mM phosphate at pH 7 + 40 mg/mL dextrose

VI: Ascorbic acid at 2 mg/mL in 20 mM citrate at pH 6 + 40 mg/mL dextrose

VII: Control (*see* WO 98/49162) : 20 mM phosphate at pH 6.8 + 50 mg/mL dextrose

VIII: Sodium bisulfite at 6.6 mg/mL in 20 mM citrate buffer at pH 6 + 40 mg/mL dextrose

IX: Sodium metabisulfite at 10 mg/mL in 20 mM citrate buffer at pH 6 + 40 mg/mL dextrose

These nine formulations were stored at ambient temperature and exposed to light for 48 hours. Samples were collected over time and submitted for HPLC analysis. A number of the formulations precipitated at some point however the study was continued for those samples. The studies were continued because the formulations which precipitated could be filtered and still tested by HPLC for % purity. The oxidation reaction produced a color change from yellow to orange so it was possible to visually assess the stability of the test formulations as well. In the end, the visual stability assessments correlated well with the HPLC data. The HPLC results are summarized in Tables 1 and 2.

Table 1. HPLC Purity Analysis of Nine Antioxidant Liquid Formulations of sitaxsentan sodium

Time Points (h)	% Total Related Peaks From Various Formulations								
	VI	III	II	I	V	IV	Control	VIII	IX
0	0.14	0.23	0.07	0.14	0.86	0.39	3.57	3.01	11.03
2	0.16	0.21	0.08	0.14	1.04	0.57	4.35	4.01	6.74
4	0.17	0.24	0.07	0.14	1.12	0.62	4.56	5.26	8.16
24	0.83	0.32	0.07	0.36	4.35	1.01	11.82	7.43	7.43
48	0.79	0.42	0.08	0.49	6.39	2.23	15.69	9.64	9.3

Table 2. HPLC Assay of Nine Antioxidant Liquid Formulations of sitaxsentan sodium

Time Points (h)	Assay as % of Label Claim of 25 mg/mL in Various Formulations								
	VI	III	II	I	V	IV	Control	VIII	IX
0	98.9	97.7	98.8	98.3	96.8	97.9	93.1	93.9	83.4
2	98.8	98.2	99.1	98.3	96.6	97.8	92.1	92.9	88.7
4	99.1	97.1	99.4	98.2	96.1	98.4	91.1	91.8	86.9
24	98.1	98.9	99.4	98.4	92.8	97	83.7	85.8	88.9
48	96.1	97.7	98.9	97.7	89.2	96.3	79.1	68.4	83.2

Table 3 contains a summary of the physical appearance of the test formulations and it can be seen that a number of them had precipitation, others experienced color changes and a few were unchanged over the course of the study.

Table 3. Physical Appearance of Sitaxsentan Sodium Formulations With Various Antioxidants. Samples Stored at Ambient Temperature and Light.

Time Points	Formulations								
	V	IV	VII	VIII	IX	VI	III	II	I
0	A	A/D	A	A	A	B	A	A	A
2 h	--	--	--	B	B	B	A	A	A
4 h	--	D	--	B	B	B	A	A	A
24 h	D	D	D	C	C	C	B	B	A
48 h	D/E	D	D/E	C/F	C/F	C	B	B	A
Final pH	6.81	7.97	6.56	5.78	5.78	6.48	6.41	6.53	6.11

A = Clear, yellow solution
B = Hazy, yellow solution
C = Hazy and/or precipitated, amber solution
D = Clear, amber solution
E = Clear, orange solution
F = Hazy and/or precipitated, orange solution

Table 4 summarizes the rank order stability of all the formulations taking into account the chemical and physical stability.

Table 4. Overall Rank Order Assessment of TBC Sitaxsentan Sodium Antioxidant Formulations Considering Chemical and Physical Stability.

Formulation #	Purity Rank	Assay Rank	Physical Stability Rank	Overall Score (Rank)
V	6	6	3	15 (5)
IV	5	4	2	11 (4)
Control	9	7	3	19 (7)
VIII	7	7	7	21 (8)
IX	7	7	7	21 (8)
VI	4	5	7	16 (6)
III	2	1	5	8 (3)
II	1	1	5	7 (2)
I	2	3	1	6 (1)

Considering all of the data, the following four formulations were carried into the lyophilization stage of the project.

I: Monothioglycerol at 10 mg/mL and disodium EDTA at 2 mg/mL in 20 mM citrate buffer at pH 6 + 40 mg/mL dextrose, lyophilized as lot IA

II: Monothioglycerol at 10 mg/mL in 20 mM citrate buffer at pH 6 + 40 mg/mL dextrose, lyophilized as lot IIA

III: Ascorbic acid at 2 mg/mL, sodium bisulfite at 6.6 mg/mL and sodium sulfite at 2 mg/mL, 20 mM citrate pH 6 + 40 mg/mL dextrose, lyophilized as lot IIIA

IV: Sodium sulfite at 2 mg/mL in 20 mM phosphate at pH 8 + 40 mg/mL dextrose, lyophilized as lot IV A

Example 3: Lyophilization Of Samples I-IV

The four formulations above were prepared for lyophilization and were run according to the cycle summarized in Table 5.

Table 5. Initial Conditions for Small Scale Lyophilization of sitaxsentan sodium Formulation with Antioxidants (Samples I-IV)

Steps	Conditions
Step1	Loading vials on shelf set to 5°C
Step 2, Freezing	Cool shelf to -40°C
Step 3, Freezing	Hold at -40°C for 4 hours
Step 4, Evacuation	Evacuate chamber to a pressure of 150 mtorr
Step 5, Primary Drying	Heat shelf to -15°C, hold pressure at 150 mtorr
Step 6, Primary Drying	Hold at -15°C and 150 mtorr for 50 hours
Step 7, Secondary Drying	Heat shelf to +25°C and 50 mtorr
Step 8, Secondary Drying	Hold at +25°C and 50 mtorr for a minimum of 6 hours

Lyophilized Formula IVA exhibited a good physical cake appearance. All four formulations were submitted for moisture and HPLC analysis. All four formulations were reconstituted and their physical stability in solution was assessed. Samples were reconstituted with 10mL of water using a needle and syringe. All samples reconstituted readily and were placed on the bench-top exposed to ambient temperature and light over a period of 48 hours (Table 6).

Table 6. Reconstitution Stability Study for Sitaxsentan Sodium Formulation with Antioxidants (Formulas IA, IIA, IIIA and IVA)

Sample	Observations / Appearance
25mg/mL sitaxsentan sodium in 20mM Phosphate Buffer (pH 8.0 +/- 0.3), 4% Dextrose with 2mg/mL Sodium Sulfite	*Observations for Formula IVA* Cake dissolves with assistance of some vortex mixing. A clear yellow / golden color solution throughout the day for first 5 h. Solution was examined the following morning at 22 h and had changed back to initial appearance of clear yellow with no ppt after 1 week of storage at ambient temperature.

Sample	Observations / Appearance
25mg/mL sitaxsentan sodium in 20mM Citrate Buffer (pH 6.0 +/- 0.3), 4% Dextrose with 10mg/mL Monothioglycerol	*Observations for Formula IIA* Cakes dissolve with hand agitation and vortex mixing. A clear light yellow solution held throughout the day for the first 5 hours. Appearance after 23 h still similar to time zero. After 28 hours of storage, the samples began to turn a slightly hazy, light yellow solution with a white ppt forming at bottom of vials.
25mg/mL sitaxsentan sodium in 20mM Citrate Buffer (pH 6.0 +/- 0.3), 4% Dextrose with 10mg/mL Monothioglycerol and 2mg/mL of EDTA	*Observations for Formula IA* Cakes dissolve with hand agitation and vortex mixing. A clear, light yellow solution at time zero held for about 1 hour. At 2 h, a haze began to appear becoming very hazy within 1 h more. At 24 h, the solution appearance was a light yellow solution with ppt settled at the bottom of the vials.
25mg/mL sitaxsentan sodium in 20mM Citrate Buffer (pH 6.0 +/- 0.3), 4% Dextrose with 2mg/mL Ascorbic Acid, 6.6mg/mL of Sodium Bisulfite, and 2mg/mL of Sodium Sulfite	*Observations for Formula IIIA* Cakes dissolve with hand agitation and vortex mixing. Samples remain clear, light yellow color throughout 24 h. No precipitation at 24 h. Solutions were clear yellow with no ppt after 1 week of storage at ambient temp.

This data indicated that formulas IVA and IIIA were physically stable over a period of days while formulas IIA and IA precipitated within 48 hours. The HPLC data on the four lyophilized formulations is summarized in Table 7.

Table 7. HPLC Analysis of Various Lyophilized Formulations of sitaxsentan sodium.

Formula Number	Formula Composition	Assay (% of LC @ 25mg/mL)	% Total Related Peaks
IVA	Sitaxsentan sodium at 25 mg/mL in 20 mM phosphate (pH 8) + 40 mg/mL dextrose + 2 mg/mL Na sulfite	92.2; 92.8	3.57; 3.28
IIA	Sitaxsentan sodium at 25 mg/mL in 20 mM citrate (pH 6) + 40 mg/mL dextrose + 10 mg/mL monothioglycerol	94.8; 97.2	0.14; 0.14
IA	Sitaxsentan sodium at 25 mg/mL in 20 mM citrate (pH 6) + 40 mg/mL dextrose + 10 mg/mL monothioglycerol + 2 mg/mL di-Na EDTA	97.7; 96.4	0.07; 0.07

Formula Number	Formula Composition	Assay (% of LC @ 25mg/mL)	% Total Related Peaks
IIIA	Sitaxsentan sodium at 25 mg/mL in 20 mM citrate (pH 6) + 40 mg/mL dextrose + 2 mg/mL ascorbic acid + 6.6 mg/mL Na bisulfite + 2 mg/mL Na sulfite	96.0; 95.8	0.08; 0.13

From the HPLC data on the four lyophilized formulations (Table VII), it was apparent that the sodium sulfite formulation at pH 8, formula IVA, was significantly less stable than the other three formulations.

Example 4: Redevelopment of Formula IIA and IA

The monothioglycerol formulations were redeveloped to eliminate the precipitation while retaining the chemical stability. A number of solution formulations were set up at ambient temperature and light looking for evidence of precipitation. The following 5 formulas were examined in this study. The sitaxsentan sodium concentration was 25 mg/mL in each formula.

1: Monothioglycerol at 10 mg/mL in 20 mM citrate buffer at pH 6 + 40 mg/mL dextrose

2: Monothioglycerol at 10 mg/mL in 20 mM citrate buffer at pH 7 + 40 mg/mL dextrose

3: Monothioglycerol at 10 mg/mL in 20 mM phosphate buffer at pH 6 + 40 mg/mL dextrose

4: Monothioglycerol at 10 mg/mL in 20 mM phosphate buffer at pH 7 + 40 mg/mL dextrose

5: Monothioglycerol at 10 mg/mL in 20 mM phosphate buffer at pH 8 + 40 mg/mL dextrose

Formula 1 precipitated in the first 24 hours of storage and the rest of formulations were unchanged. Formula 3 precipitated approximately after 28 hours, thus indicating that the initial pH is an important factor in stabilizing the monothioglycerol formulations. The formulas at pH 7 and 8 were stable throughout longer periods of storage (> 48 hours) and it seems that any of them would be acceptable to carry into lyophilization. Placebo solutions (no sitaxsentan sodium) of each formulation were monitored along

with each active formula in order to learn more about the precipitation problem. None of the placebos precipitated indicating that the precipitate involves the sitaxsentan sodium.

Example 5. Lyophilization Studies of Formula 2 and 4

Formula 2 and 4 were lyophilized according to the cycle in Table 8.

Table 8. Conditions for Lyophilization of 25mg/mL Sitaxsentan Sodium in 20mM Citrate Buffer (pH 7.0 ± 0.3)) (formulation 2A) and in 20mM Phosphate Buffer (pH 7.0 ± 0.3),4% Dextrose with 10mg/mL Monothioglycerol (formulation 4A)

Steps	Conditions
Step1	Loading vials on shelf set to 5°C
Step 2, Freezing	Cool shelf to -45°C
Step 3, Freezing	Hold at -45°C for 4 hours
Step 4, Evacuation	Evacuate chamber to a pressure of 150 mtorr
Step 5, Primary Drying	Heat shelf to -15°C for 1 hour, hold pressure at 150 mtorr
Step 6, Primary Drying	Hold at -15°C and 150 mtorr for 70 hours
Step 7, Secondary Drying	Heat shelf to +25°C for a period of 80 minutes and 50 mtorr
Step 8, Secondary Drying	Hold at +25°C and 50 mtorr for a minimum of 6 hours

The physical appearance of both formulations was acceptable. The reconstitution of both formulations was good (< 2 minutes). An effort was made to improve the cake appearance of the formulations by revising the lyophilization cycle. A lower freezing temperature (-45°C) and lower primary drying temperatures (-20°C and -25°C) were tested and resulted in some improvement in cake appearance.

Example 6: Prototype Stability Study With Formula 4

Formula 4A was selected for prototype stability and was manufactured at a scale of 135 vials according to the cycle shown in Table 9. The conditions in Table 9 were selected in an effort to eliminate cake shrinkage that occurred during primary drying. Thus an extra primary drying step of -5°C was added to the cycle.

Table 9. Conditions for Lyophilization of 25mg/mL Sitaxsentan Sodium in 20mM Phosphate Buffer (pH 7.0 ± 0.3), 4% Dextrose with 10mg/mL Monothioglycerol for Prototype Stability

Steps	Conditions
Step1	Loading vials on shelf set to 5°C
Step 2, Freezing	Cool shelf to -40°C over a period of 1 hour
Step 3, Freezing	Hold at -40°C for 4 hours
Step 4, Evacuation	Evacuate chamber to a pressure of 150 mtorr

Steps	Conditions
Step 5, Primary Drying	Heat shelf to -15°C over a period of 50 minutes, hold pressure at 150 mtorr
Step 6, Primary Drying	Hold at -15°C and 150 mtorr for 70 hours
Step 7, Primary Drying	Heat shelf to -5°C over 20 minutes, hold pressure at 150 mtorr
Step 8, Primary Drying	Hold at -5°C and 150 mtorr for 4 hours
Step 9, Secondary Drying	Heat shelf to +25°C over 1 hour, and 50 mtorr
Step 10, Secondary Drying	Hold at +25°C and 50 mtorr for a minimum of 6 hours

The formulations containing dextrose became difficult to reconstitute after storage and therefore was changed to corresponding formulations containing mannitol as described in Example 7.

Example 7: Formulations Containing mannitol

Formulation A: Sitaxsentan sodium at 25 mg/mL, ascorbic acid at 2 mg/mL, sodium bisulfite at 6.6 mg/mL and sodium sulfite at 2 mg/mL in 20 mM citrate pH 6 + mannitol at 20 mg/mL, lyophilized as shown below (Table 10):

Table 10: Lyophilization Conditions for formulation A

Steps	Conditions
Step1	Loading vials on shelf set to 5°C
Step 2, Freezing	Cool shelf to -40°C
Step 3, Freezing	Hold at -40°C for 4 hours
Step 4, Evacuation	Evacuate chamber to a pressure of 150 mtorr
Step 5, Primary Drying	Heat shelf to -15°C, hold pressure at 150 mtorr
Step 6, Primary Drying	Hold at -15°C and 150 mtorr for 50 hours
Step 7, Secondary Drying	Heat shelf to +25°C and 50 mtorr
Step 8, Secondary Drying	Hold at +25°C and 50 mtorr for a minimum of 6 hours

Formulation B: Staxsentan sodium at 25 mg/mL and monothioglycerol at 10 mg/mL in 20 mM phosphate buffer at pH 7 + mannitol at 20 mg/mL, lyophilized as shown below (Table 11):

Table 11: Lyophilization Conditions for formulation B

Steps	Conditions
Step1	Loading vials on shelf set to 5°C
Step 2, Freezing	Cool shelf to -40°C over a period of 1 hour

Steps	Conditions
Step 3, Freezing	Hold at -40°C for 4 hours
Step 4, Evacuation	Evacuate chamber to a pressure of 150 mtorr
Step 5, Primary Drying	Heat shelf to -15°C over a period of 50 minutes, hold pressure at 150 mtorr
Step 6, Primary Drying	Hold at -15°C and 150 mtorr for 70 hours
Step 7, Primary Drying	Heat shelf to -5°C over 20 minutes, hold pressure at 150 mtorr
Step 8, Primary Drying	Hold at -5°C and 150 mtorr for 4 hours
Step 9, Secondary Drying	Heat shelf to +25°C over 1 hour, and 50 mtorr
Step 10, Secondary Drying	Hold at +25°C and 50 mtorr for a minimum of 6 hours

Example 8. A Solution Stability Study To Determine The Effect Of Antioxidants: Ascorbic Acid and Monothioglycerol

Stability of three formulations containing ascorbic acid or monothioglycerol was studied. Sitaxsentan sodium was present at 25 mg/mL in each of the following formulations:

8a: Ascorbic acid at 4.0 mg/mL + 20 mM citrate buffer at pH 6.8 +/-0.1

8b: Ascorbic acid at 4.0 mg/mL + 20 mM phosphate buffer at pH 6.8 +/-0.1

8c: Monothioglycerol at 4.0 mg/mL in 20 mM phosphate buffer at pH 6.8 +/-0.1

The formulations were lyophilized according to lyophilization cycle as follows: The batch was frozen to -45°C. The vacuum was started and controlled at 30 microns and then the shelf temperature was warmed to +20°C over 10 hours and then held there until the cycle was competed based on moisture of the batch.

The lyophilized formulations were reconstituted and stored at ambient temperature and exposed to light for 48 hours. Samples were collected over time and submitted for HPLC analysis. The HPLC results are summarized in Table 8a.

Formulation	Buffer	Excipients	mg/mL	Total Related Products (t=0)	Total Related Products (4 h)	Total Related Products (24 h)	Total Related Products (48 h)
8a	Citrate	Ascorbic Acid	4.0	0.22	0.41	0.49	1.19
8b	Phosphate	Ascorbic Acid	4.0	0.07	0.24	0.42	0.85
8c	Phosphate	Monothioglycerol	4.0	0.21	0.21	0.25	0.38

B. Oral Tablet Formulations:

Example 9: Excipient compatibility study for tablet formulations

This study was designed to evaluate the effects of various diluents, binders, disintegrants, lubricants, buffering agents, and antioxidants on the stability of the drug substance. Binary mixtures of sitaxsentan sodium with various functional excipients were prepared by placing the requisite amount of drug and excipient in 20 mL glass vials and vortexing the vials for 10-15 seconds to mix the contents. These vials were opened and stored at 40°C/75%RH and tested after two and four week periods. The results in Table 12 demonstrate that, among the excipients tested, BHA, propyl gallate, and Tween 80 caused significant degradation of the drug substance. Colloidal silicon dioxide also caused significant instability to sitaxsentan sodium (86.8% drug remaining and 11.96% total related substances after four weeks at 40°C/75%RH). In addition, the following excipients promoted the degradation of the drug: dextrates, mannitol, PVP, BHT, and alpha tocopherol (greater than 1.0% total related substances and/or reduced assay after four weeks at 40°C/75%RH). These excipients were excluded from the further development studies of the tablets.

Table 12: Drug-Excipient Compatibility Study Results (40°C/75%RH Open Bottle)

Excipient Type	Excipient	Drug/ Excipient (wt/wt)	Assay (%)		Total Related Substanes (%)	
			T=2 Weeks	T=4 Weeks	T=2 Weeks	T=4 Weeks
Drug Control 1	Sitaxsentan Sodium	N/A	100.7	100.8	0.19	0.24
Drug Control 2	Sitaxsentan Sodium	N/A	98.0	100.9	0.18	0.12
Diluents/Fillers	Lactose Monohydrate (Fast-Flo)	1:2	99.3	100.3	0.28	0.45
	Calcium Phosphate Dibasic	1:2	101.5	98.9	0.49	0.64
	Microcrystalline Cellulose (Avicel PH-102)	1:2	100.0	99.0	0.63	0.97
	Dextrates (Emdex)	1:2	97.3	97.0	0.99	1.94
	Mannitol	1:2	96.8	90.0	2.82	3.97
Binder/Diluent	Pregelatinized Starch	1:2	98.3	99.6	0.21	0.31
Binders	Hydroxypropyl Methylcellulose (Methocel E5P)	1:1	99.8	99.4	0.28	0.26
	Hydroxypropyl Cellulose	1:1	99.8	98.5	0.39	0.83
	Polyvinylpyrrolidone (PVP K29/32)	1:1	97.9	94.7	1.58	3.80
Disintegrants	Sodium Croscarmellose (Ac-Di-Sol)	1:1	101.1	99.1	0.27	0.22
	Sodium Starch Glycolate (Explotab)	1:1	101.0	100.9	0.19	0.30
Glidant/Lubricant	Magnesium Stearate	1:1	100.2	101.3	0.18	0.15

Excipient Type	Excipient	Drug/ Excipient (wt/wt)	Assay (%)		Total Related Substanes (%)	
			T=2 Weeks	T=4 Weeks	T=2 Weeks	T=4 Weeks
	Powdered Cellulose	1:1	97.8	100.6	0.23	0.33
	Colloidal Silicon Dioxide	1:1	89.9	86.8	8.99	11.96
Buffering Agents	Sodium Phosphate Monobasic	2:1	98.9	99.3	0.21	0.53
	Sodium Phosphate Dibasic	2:1	99.2	99.3	0.16	0.20
Antioxidant	Sodium Ascorbate	2:1	99.6	99.8	0.18	0.18
	Glycine	2:1	99.4	99.2	0.16	0.19
	Sodium Metabisulfite	2:1	98.2	99.3	0.11	0.24
	Ascorbyl Palmitate	2:1	100.1	100.5	0.18	0.20
	Disodium EDTA	2:1	100.3	100.9	0.23	0.26
	BHT	2:1	100.2	100.4	1.00	1.03
	Alpha Tocopherol	2:1	97.2	96.2	0.95	2.57
	BHA	2:1	77.4	47.6	18.43	44.95
	Propyl Gallate	2:1	64.0	ND[1]	53.91	ND
Other	Tween 80	2:1	79.2	ND	14.63	ND

[1] Not determined

Based on drug-excipient compatibilities, processibility, and ability to produce a tablet with satisfactory hardness and friability, lactose monohydrate and microcrystalline cellulose were chosen as diluents, hydroxypropyl methylcellulose was chosen as the binder for sitaxsentan sodium coated tablets.

Example 10: Effect of coating on tablet formulations

Drug Stability of coated tablets containing initial prototype formulation B (Table 13) was compared to the uncoated formulation A at 40°C/75%RH.

Table 13: Initial Prototype Formulation B

Component	mg per Tablet	% w/w
Intragranular Components		
Sitaxsentan Sodium	100.0	20.0
Microcrystalline Cellulose (Avicel PH-102)	175.0	35.0
Lactose Monohydrate Fast-Flo	84.3	16.9
Hydroxypropyl Methylcellulose 2910	25.0	5.0
Ascorbyl Palmitate	0.5	0.1
Sodium Starch Glycolate (Explotab)	12.5	2.5
Granulating Agents		
Sodium Phosphate Monobasic Monohydrate Granular AR	0.6	0.1
Sodium Phosphate Dibasic Anhydrous Gen	1.1	0.2
Disodium Edetate Dihydrate Gen AR	0.5	0.1
Purified Water[1]		
Extragranular Components		
Lactose Monohydrate Fast-Flo	83.0	16.6
Sodium Starch Glycoloate (Explotab)	12.5	2.5
Magnesium Stearate (Non-Bovine #5712)	5.0	1.0
Total Core Tablet Weight	**500.0**	**100.0**

[1] In-process agent; it is removed during the process.

Formulation A, High Shear Granulation Process

Component	mg per Tablet
Intragranular Components	
Sitaxsentan Sodium	100.0
Microcrystalline Cellulose (Avicel PH-102)	255.8
Dibasic Calcium Phosphate	90.0
Hydroxypropyl Cellulose	20.0
Sodium Phosphate Monobasic Monohydrate	0.6
Sodium Phosphate Dibasic	1.1
Sodium Starch Glycolate (Explotab)	12.5
Purified Water1	
Extragranular Components	
Collodial Silicon Dioxide	2.5
Sodium Starch Glycolate (Explotab)	12.5
Magnesium Stearate (Non-Bovine #5712)	5.0
Total Core Tablet Weight	**500.0**

1. In-process agent. It is removed during the process.

Table 14: Drug Stability of Initial Prototype Formulation as Compared to the Original Formulation, Crushed Uncoated Tablets in Open Bottles at 40°C/75%RH

Formulation	T=0		T=2 Weeks		T=4 Weeks	
	Assay (%)	TRS[1] (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)
Uncoated formulation	100.0	0.20	96.4	3.41	89.2	5.77
Prototype coated formulation	97.7	0.06	92.6	0.70	91.5	1.46

[1] Total related substances

As seen in Table 14, the prototype coated formulation B has improved stability as compared to the uncoated formulation A.

Example 11: Effect of antioxidants

Various types of antioxidants were evaluated in the drug-excipient compatibility study (Example10). Among the nine antioxidants evaluated, sodium ascorbate, glycine, sodium metabisulfite, ascorbyl palmitate, and disodium edetate (EDTA) were found to be compatible with the drug. The combination of ascorbyl palmitate and EDTA was chosen based on the results from the excipient compatibility studies and tablet storage stability studies. Further evaluations were conducted out to study the effects of various

levels of ascorbyl palmitate (0.1%, 0.2%, and 2.0%) and EDTA (0.1% and 0.2%) on drug stability. As shown in Table 15, the formulation containing 0.2% of ascorbyl palmitate and 0.2% of EDTA is most stable over time.

Table 15: Effect of Antioxidant Concentration on the Stability of Sitaxsentan Sodium 100 mg Uncoated Tablets in Open Bottles at 40°C/75%RH

Levels of Antioxidants		Tablet Batch Number	T=0		T=2 Weeks		T=4 Weeks		T=8 Weeks		T=12 Weeks	
Ascorbyl Palmitate	EDTA		Assay (%)	TRS[1] (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)
0.1	0.1	C	97.7	0.06	95.1	0.51	94.2	1.26	92.5	2.41	89.8	3.58
0.2	0.2	D	99.1	0.10	97.8	0.33	96.3	0.58	94.5	1.25	94.2	1.97
2.0	0.1	E	98.8	0.12	95.6	1.15	96.5	1.52	93.3	2.35	93.1	3.29

[1] Total related substances

Formulation C, D and E with Various Levels of Antioxidants (mg per Tablet)			
Component	**C**	**D**	**E**
Intragranular Components			
Sitaxsentan Sodium	100.0	100.0	100.0
Microcrystalline Cellulose (Avicel PH-102)	175.0	175.0	175.0
Lactose Monohydrate Fast-Flo	84.3	84.3	84.3
Hydroxypropyl Methylcellulose 2910	25.0	25.0	25.0
Ascorbyl Palmitate	0.5	1.0	10.0
Sodium Starch Glycolate (Explotab)	12.5	12.5	12.5
Sodium Phosphate Monobasic Monohydrate Granular AR	0.6	0.6	0.6
Sodium Phosphate Dibasic Anhydrous Gen	1.1	1.1	1.1
Disodium Edetate Dihydrate Gen AR	0.5	1.0	0.5
Purified Water1			
Extragranular Components			
Lactose Monohydrate Fast-Flo	83.0	82.0	73.5
Sodium Starch Glycolate (Explotab)	12.5	12.5	12.5
Magnesium Stearate (Non-Bovine #5712)	5.0	5.0	5.0
Total Core Tablet Weight	**500**	**500**	**500**
1. In-process agent. It is removed during the process.			

Test Method: HPLC with a Diode Array detector (264 nm and 240 nm).

Column: phenomenex Luna C18 (2) 4.6 mm x 150 mm, 5 micron particles.

Mobil Phases: 50 mN H_3PO_4 at pH 3.5 and Methanol.

Example 12: Effect of Buffers

A buffer agent mixture is used to improve drug stability in the tablets. A sodium phosphate monobasic (0.1% wt/wt) and sodium phosphate dibasic (0.2% wt/wt) buffer mixture (buffer pH 6.8) was found to improve the drug stability relative to the control tablet without the buffer salts (Table 16). Therefore, the buffer salts mixture was used in the formulation to control the microenvironment of the drug substance during the granulation process and in the resulting tablet.

Table 16: Effect of Buffering Salts on the Stability of Sitaxsentan Sodium 100 mg Uncoated Tablets in Open Bottles at 40°C/75%RH

Buffer Agent	Tablet Batch Number	T=0		T=2 Weeks		T=1 Month		T=2 Months	
		Assay (%)	TRS[1] (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)
0.1% Sodium Phosphate Monobasic and 0.2% Sodium Phosphate Dibasic (Uncoated Tablet)	F	99.3	0.39	97.9	0.49	96.4	1.25	94.0	2.55
No Buffer Control (4% Sepifilm®/Sepisperse Coating)	G	98.3	0.42	95.3	1.10	92.6	2.40	88.4	4.08

[1] Total related substances

Table 17: Formulation F and G With and Without Buffer Agents

Component	mg per Tablets	
	F	G
Intragranular Components		
Sitaxsentan Sodium	100.0	100.0
Microcrystalline Cellulose (Avicel PH-102)	175.0	175.0
Lactose Monohydrate Fast-Flo	84.3	84.3
Hydroxypropyl Methylcellulose 2910	25.0	25.0
Ascorbyl Palmitate	0.5	10.0
Sodium Starch Glycolate (Explotab)	12.5	12.5
Sodium Phosphate Monobasic Monohydrate Granular AR	0.6	0.0
Sodium Phosphate Dibasic Anhydrous Gen	1.1	0.0
Disodium Edetate Dihydrate Gen AR	0.5	0.5
Purified Water[1]		
Extragranular Components		
Lactose Monohydrate Fast-Flo	83.0	84.7
Sodium Starch Glycolate (Explotab)	12.5	12.5

Magnesium Stearate (Non-Bovine #5712)	5.0	5.0
Total Core Tablet Weight	**500**	**500**

1. In-process agent. It is removed during the process.

Example 13: Effect of Coating

Four types of coatings were initially evaluated, Sepifilm® LP014/Sepisperse Dry 3202 Yellow, Blue Opadry, Eudragit EPO and Opadry AMB. The main objective was to identify a coating that would serve as a moisture barrier to further hinder oxidation of sitaxsentan sodium. Among the four types of coating materials evaluated, Sepifilm® LP014/Sepisperse Dry 3202 Yellow (Sepifilm®/Sepisperse) (3/2 wt/wt) at a 4% tablet weight gain and Blue Opadry at 3% tablet weight gain both produced a uniform smooth coating. Sepifilm® LP014/Sepisperse Dry 3202 Yellow (Sepifilm®/Sepisperse) (3/2 wt/wt) at a 4% tablet weight gain was selected because of its good processibility.

Table 18: Effect of Coating on the Stability of Sitaxsentan Sodium 100 mg Tablets in Open Bottles at 40°C/75%RH (Test Method described Example 11)

Formulation	T=0		T=2 Weeks		T=4 Weeks		T=8 Weeks		T=12 Weeks	
	Assay (%)	TRS[1] (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)
C Uncoated	97.7	0.06	95.1	0.51	94.2	1.26	92.5	2.41	89.8	3.58
H 4% Opadry AMB	97.9	0.11	96.3	0.57	93.7	1.51	91.9	2.70	90.4	4.26
I 4% Eudragit EPO	95.6	0.11	94.7	0.62	92.3	1.76	90.6	3.30	87.8	4.77
J 4% Sepifilm®/Sepisperse	97.9	0.10	95.1	0.43	94.6	1.22	91.9	2.39	89.5	3.46

[1] Total related substances

Formulation have the same tablet core as tablet C. Coating are different as descriped in Table 18.

Example 14: Sitaxsentan 100 mg Coated Tablets

The tablets were manufactured on a one kg scale. The granulating solution was prepared by dissolving sodium phosphate, mono- and di-basic, and disodium EDTA in purified water. Ascorbyl palmitate was added to the sitaxsentan sodium drug substance and blended in a bag by hand for approximately 30 seconds. Approximately half of the microcrystalline cellulose was added to the bag and blended for an additional 30 seconds. The mixture was screened through a screen. The remaining intragranular components (i.e., remaining microcrystalline cellulose, lactose, HPMC, sodium starch

glycolate) were screened through a screen and added to the mixture. The powders were then charged into a heated Glatt GPCG-1. The granulating solution was applied to the intragranular powders. Additional water was sprayed, if necessary, to achieve a visually desirable granulation. After that, the granulation was dried until an LOD of less than 2% was achieved. The dried granulation was milled through a Fitzmill with a 0.0024-sized screen. Extragranular components were screened and blended with the milled granulation in an 8-qt. V-blender for five minutes. Magnesium stearate was screened then blended with the mixture for three minutes. The final blends were compressed on a tablet press to 500 mg core tablets using 0.2900" x 0.6550" modified oval tooling.

Coating suspension was prepared by adding Sepifilm® LP014 and Sepisperse Dry 3202 (Yellow) to water with mixing. Mixing continued until a homogenous suspension is formed. The tablets were coated using a Compu-lab coater with a 19" coating pan.

Table 19. Sitaxsentan Sodium 100 mg Clinical Tablet Formulation

Component	mg/tablet	% w/w
Sitaxsentan sodium	100.0	20.0
Microcrystalline Cellulose (Avicel PH 102)	175.0	35.0
Lactose Monohydrate Fast Flo (intragranular)	84.3	16.9
Lactose Monohydrate Fast Flo (extragranular)	82.0	16.4
Hydroxypropyl Cellulose E-5P	25.0	5.0
Ascorbyl Palmitate	1.0	0.2
EDTA, Disodium	1.0	0.2
Sodium Phosphate, Monobasic Monohydrate	0.6	0.1
Sodium Phosphate, Dibasic Anhydrous	1.1	0.2
Sodium Starch Glycolate (intragranular)	12.5	2.5
Sodium Starch Glycolate (extragranular)	12.5	2.5
Magnesium Stearate, Non-Bovine	5.0	1.0
Purified Water, USP	192.5	---
Total Core Tablet Weight	500.0	100.0
Sepisperse Dry 3202 (Yellow)	8.0	1.6
Sepifilm® LP 014	12.0	2.4
Total Coated Tablet Weight	520.0	104.0

Example 15: Comparison between the uncoated tablet core and the coated tablet

Comparison between the uncoated tablet core and the coated tablet, prepared by the method of Example 14, was conducted to determine the effect of the Sepifilm®/Sepisperse moisture barrier.

Table 20: Stability Results of the Formulation for Sitaxsentan Sodium 100 mg Uncoated Tablet Core

Storage Conditions	T=0		T=1 Month		T=3 Months		T=6 Months	
	Assay (%)	TRS[1] (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)
25°C/60%RH[2]	100.0	0.06	101.9	0.00	98.9	0.00	99.3	0.27
40°C/75%RH	100.0	0.06	97.7	0.00	98.0	0.29	95.5	1.66

[1] Total related substances
[2]Relative humidity

Table 21: Stability Results of the Formulation for Sitaxsentan Sodium 100 mg Coated Tablet Core

Storage Conditions	T=0		T=1 Month		T=2 Months		T=3 Months		T=6 Months	
	Assay (%)	TRS1 (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)	Assay (%)	TRS (%)
25°C/60%RH[2]	99.5	0.00	98.5	0.00	99.5	0.00	98.6	0.00	98.2	0.23
40°C/75%RH	99.5	0.00	98.3	0.05	97.8	0.06	98.4	0.32	98.2	1.02

[1] Total related substances
[2]Relative humidity

As seen from the results in Tables 20 and 21 above, the Sepifilm®/Sepisperse coating provides additional protection for the drug substance in the tablet.

All of the references cited herein are incorporated by reference in their entirety. While the invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the invention as recited by the appended claims.

The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

What is claimed is:

1. A lyophilized powder comprising sitaxsentan sodium, an antioxidant, a buffer and a bulking agent.

2. The lyophilized powder of claim 1, wherein the sitaxsentan sodium is present in an amount from about 20% to about 50% by total weight of the lyophilized powder.

3. The lyophilized powder of claim 1, wherein the amount of sitaxsentan sodium is about 41% by total weight of the lyophilized powder.

4. The lyophilized powder of any of claims 1-3, wherein the antioxidant is sodium sulfite, sodium bisulfite, sodium metasulfite, monothioglycerol, ascorbic acid or a combination thereof.

5. The lyophilized powder of any of claims 1-4, wherein the antioxidant is monothioglycerol.

6. The lyophilized powder of any of claims 1-4, wherein the antioxidant is a combination of ascorbic acid, sodium sulfite and sodium bisulfite.

7. The lyophilized powder of any of claims 4 or 5, wherein the monothioglycerol in the lyophilized powder is present in an amount ranging from about 10% to about 30% by total weight of the lyophilized powder.

8. The lyophilized powder of claims 4 or 6, wherein the ascorbic acid is present in an amount from about 1% to about 5% by total weight of the lyophilized powder.

9. The lyophilized powder of any of claims 4, 6 or 8, wherein the amount of ascorbic acid is about 3.3% by total weight of the lyophilized powder.

10. The lyophilized powder of claims 4 or 6, wherein the sodium sulfite is present in an amount from about 1% to about 5% by total weight of the lyophilized powder.

11. The lyophilized powder of claims 4 or 6, wherein the amount of sodium sulfite is about 3.3% by total weight of the lyophilized powder.

12. The lyophilized powder of claims 4 or 6, wherein the sodium bisulfite is present in an amount from about 5% to about 20% by total weight of the lyophilized powder.

13. The lyophilized powder of claims 4 or 6, wherein the amount of sodium bisulfite is about 10.8% by total weight of the lyophilized powder.

14. The lyophilized powder of claim 4, wherein the amount of ascorbic acid is about 2 mg, sodium sulfite is about 3.3% and sodium bisulfite is about 10.8% by total weight of the lyophilized powder.

15. The lyophilized powder of any of claims 1-14, wherein the buffer is a phosphate or citrate buffer.

16. The lyophilized powder of any of claims 1-14, wherein the buffer is sodium citrate dihydrate.

17. The lyophilized powder of claim 15, wherein the amount of sodium citrate dihydrate is about 8.8 % by the total weight of the lyophilized powder.

18. The lyophilized powder of any of claims 1-17, wherein the bulking agent is selected from a sugar, a polyalcohol, an amino acid, a polymer and a polysaccharide.

19. The lyophilized powder of any of claims 1-17, wherein the bulking agent is sorbitol, mannitol or dextrose.

20. The lyophilized powder of claim 18, wherein the bulking agent is dextrose.

21. The lyophilized powder of claim 19 or 20, wherein the dextrose is present in an amount ranging from about 15% to about 50% by total weight of the lyophilized powder.

22. The lyophilized powder of claim 19, wherein the sugar is mannitol.

23. The lyophilized powder of claims 18 or 22, wherein the mannitol is present in an amount ranging from about 15% to about 45% by total weight of the lyophilized powder.

24. The lyophilized powder of any of claims 18, 22 or 23, wherein the amount of mannitol is about 32.8% by total weight of the lyophilized powder.

25. The lyophilized powder of any of claims 1-24, comprising about 41% of sitaxsentan sodium, about 3.3% ascorbic acid, about 3.3% sodium sulfite and about 10.8% sodium bisulfite, about 8.8% sodium citrate dihydrate and about 32.8% mannitol.

26. The lyophilized powder of any of claims 1-24, comprising about 33% of sitaxsentan sodium, about 5.3% ascorbic acid, about 7.6% sodium citrate dihydrate, about 53% D-mannitol and about 0.13% citric acid monohydrate by total weight of the lyophilized powder.

27. The lyophilized powder of any of claims 1-24, comprising about 34% of sitaxsentan sodium, about 5.5% ascorbic acid, about 3.7% sodium phosphate dibasic heptahydrate, about 55% D-mannitol and about 1.9% sodium phosphate monobasic monohydrate by total weight of the lyophilized powder.

28. A reconstituted formulation of sitaxsentan sodium, wherein the reconstituted solution comprises the lyophilized powder of any of claims 1-27.

29. The reconstituted formulation of claim 28, wherein the formulation has a pH from about 5 to about 10.

30. The reconstituted formulation of claim 28, wherein the formulation has a pH of about 6.

31. The reconstituted formulation of claim 28, wherein the formulation has a pH of about 6.8.

32. An oral tablet comprising sitaxsentan sodium, an antioxidant, a binding agent, a diluent, a buffer and a moisture resistant coating.

33. The oral tablet of claim 32, wherein the sitaxsentan sodium is present in an amount ranging from about 5% to about 40% of the total weight of the tablet.

34. The oral tablet of claims 32 or 33, wherein the amount of sitaxsentan sodium is from about 15% to about 25% of the total weight of the tablet.

35. The oral tablet of any claims 32-34, wherein the amount of sitaxsentan sodium is from about 20% of the total weight of the tablet.

36. The oral tablet of any of claims 32-35, wherein the amount of sitaxsentan sodium is about 100 mg.

37. The oral tablet of any of claims 32-36, wherein the antioxidant is a combination of ascorbyl palmitate and EDTA, disodium.

38. The oral tablet of claim 37, wherein the ascorbyl palmitate is present in an amount ranging from about 0.05% to about 3% of the total weight of the tablet.

39. The oral tablet of claim 38, wherein the amount of ascorbyl palmitate is about 0.2% of the total weight of the tablet.

40. The oral tablet of claim 38, wherein the ascorbyl palmitate is present in an amount ranging from about 0.1 mg to about 5 mg.

41. The oral tablet of claim 38, wherein the amount of ascorbyl palmitate is about 1 mg.

42. The oral tablet of claim 37, wherein the EDTA, disodium is present in an amount ranging from about 0.05% to about 3% of the total weight of the tablet.

43. The oral tablet of claim 42, wherein the amount of EDTA, disodium is about 0.2% of the total weight of the tablet.

44. The oral tablet of claim 37-43, wherein the EDTA, disodium is present in an amount ranging from about 0.1 mg to about 5 mg.

45. The oral tablet of claim 44, wherein the amount of EDTA, disodium is about 1 mg.

46. The oral tablet of any of claims 32-45, wherein the diluent comprises a combination of lactose monohydrate fast flo as an intragranular component and lactose monohydrate fast flo as an extragranular component.

47. The oral tablet of claim 46, wherein the intragranula lactose monohydrate fast flo is in an amount from about 5% to about 30% and the extragranular lactose monohydrate fast flo is in an amount from about 5% to about 30% of the total weight of the tablet.

48. The oral tablet of claim 43, wherein the amount of intragranular lactose monohydrate fast flo is about 16.9% and the amount of extragranular lactose monohydrate fast flo is about 16.4% of the total weight of the tablet.

49. The oral tablet of claim 43, wherein the amount of intragranular lactose monohydrate fast flo is about 84.3 mg and the amount of extragranular lactose monohydrate fast flo is about 82 mg.

50. The oral tablet of any of claim 32-49, further comprising microcrystalline cellulose in an amount from about 10% to about 50% of the total weight of the tablet.

51. The oral tablet of claim 50, wherein the amount of microcrystalline cellulose is about 35% of the total weight of the tablet.

52. The oral tablet of any of claim 50-51, wherein the amount of microcrystalline cellulose is from about 130 mg to about 300 mg.

53. The oral tablet of any of claim 50-52, wherein the amount of microcrystalline cellulose is about 175 mg.

54. The oral tablet of any of claim 32-53, wherein the binding agent is hydroxypropyl methylcellulose (E-5P).

55. The oral tablet of claim 54, wherein hydroxypropyl methylcellulose (E-5P) is in an amount raging from about 10% to about 50% of the total weight of the tablet.

56. The oral tablet of claim 55, wherein the amount of hydroxypropyl methylcellulose (E-5P) is about 5% of the total weight of the tablet.

57. The oral tablet of any of claims 55-56, wherein the amount of hydroxypropyl methylcellulose (E-5P) is about 25 mg.

58. The oral tablet of any of claims 32-57, wherein the moisture resistant coating comprises hydroxypropylmethylcellulose from about 1% to about 6% of the total weight of the tablet.

59. The oral tablet of claim 54, wherein the coating comprises hydroxypropylmethylcellulose from about 8 mg to about 12 mg per tablet.

60. The oral tablet of claim 29, wherein the tablet comprises sitaxsentan sodium; microcrystalline cellulose; lactose monohydrate fast flo; hydroxypropyl methylcellulose E-5P; ascorbyl palmitate; disodium EDTA; sodium phosphate monobasic, monohydrate; sodium phosphate dibasic, anhydrous; sodium starch glycoloate; magnesium stearate and a moisture resistant coating of hydroxypropylmethylcellulose.

61. The oral tablet of claim 29, wherein the tablet comprises about 20% sitaxsentan sodium; about 35% microcrystalline cellulose; about 16.9% intragranular lactose monohydrate fast flo; about extragranular 16.4% lactose monohydrate fast flo; about 5.0% hydroxypropyl methylcellulose E-5P; about 0.2% ascorbyl palmitate; about 0.2% disodium EDTA; about 0.1% sodium phosphate monobasic, monohydrate; about 0.2% sodium phosphate dibasic, anhydrous; about 2.5 % extragranular sodium starch glycoloate; about 2.5 % intragranular sodium starch glycoloate; about 1 % magnesium stearate and a moisture resistant coating of hydroxypropylmethylcellulose at about 2.4 %/1.6% weight gain.

62. The oral tablet of claim 29, wherein the tablet comprises about 100 mg sitaxsentan sodium; about 1.0 mg ascorbyl palmitate; about 1.0 mg disodium edetate, EDTA; about 25 mg hydroxypropyl methylcellulose E-5P; about 84.3 intragranular lactose monohydrate fast flo; about 82 mg extragranular lactose monohydrate fast flo; about 175 mg microcrystalline cellulose; about 0.6 mg sodium phosphate monobasic, monohydrate; about 1.1 mg sodium phosphate dibasic, anhydrous; about 12.5 mg

extragranula sodium starch glycoloate, about 12.5 mg intragranular sodium starch glycoloate; about 5 mg magnesium stearate and a moisture resistant coating of hydroxypropylmethylcellulose at about 20 mg.

63. A combination, comprising the formulation of any of claims 1-31 and a sterile vessel containing a single dosage or multiple dosage amount thereof.

64. The combination of claim 63, wherein the vessel is an ampoule, vial or syringe.

65. A pharmaceutical composition formulated for single dosage or multiple dosage administration prepared by mixing a single dosage of the formulation of any of claims 1-31 with an aqueous medium.

66. A method for the treatment of an endothelin-mediated disease, comprising administering an effective amount of the formulation of any of claim 1-65.

67. The method of claim 66, wherein the disease is selected from the group consisting of hypertension, cardiovascular disease, asthma, pulmonary hypertension, inflammatory diseases, ophthalmologic disease, menstrual disorders, obstetric conditions, wounds, gastroenteric disease, renal failure, immunosuppressant-mediated renal vasoconstriction, erythropoietin-mediated vasoconstriction endotoxin shock, anaphylactic shock and hemorrhagic shock.

68. An article of manufacture comprising packaging material and a formulation of any of claim 1-65, contained within the packaging material, wherein the packaging material includes a label that indicates that the formulation is used for treating an endothelin mediated disorder.

69. A process for preparing a lyophilized powder, comprising:

mixing sitaxsentan sodium with a solution comprising an antioxidant, a buffer and a sugar to produce a solution thereof; and

lyophilizing the solution to produce a powder.

70. An oral tablet comprising sitaxsentan sodium and a buffer.

71. An oral tablet comprising sitaxsentan sodium and a moisture barrier coating.

72. An oral tablet comprising sitaxsentan sodium and an antioxidant.

Figure 1

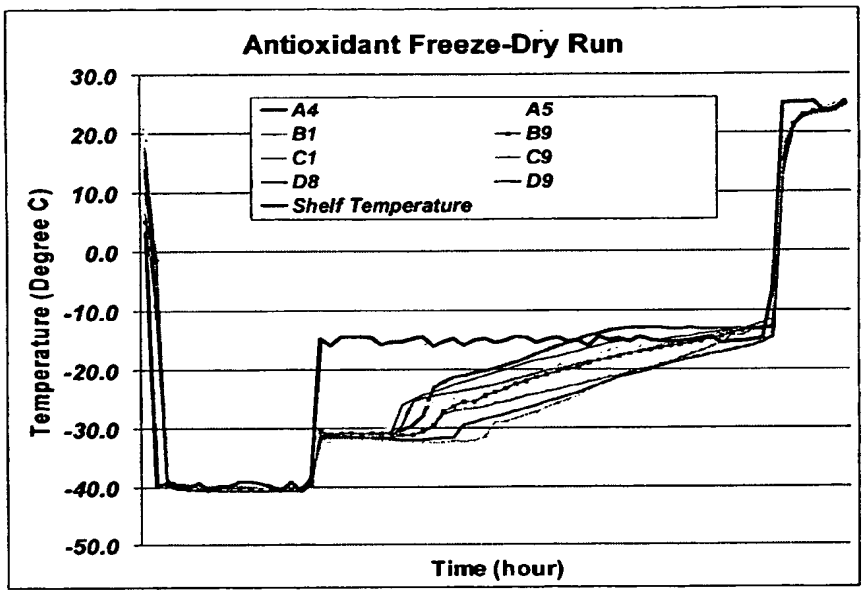

Antioxidant Freeze-Dry Run
30.0
20.0
10.0
0.0
-10.0
-20.0
-30.0
-40.0
-50.0
Temperature (Degree C)
Time (hour)
A4
B1
C1
D8
Shelf Temperature
A5
B9
C9
D9

Figure 2

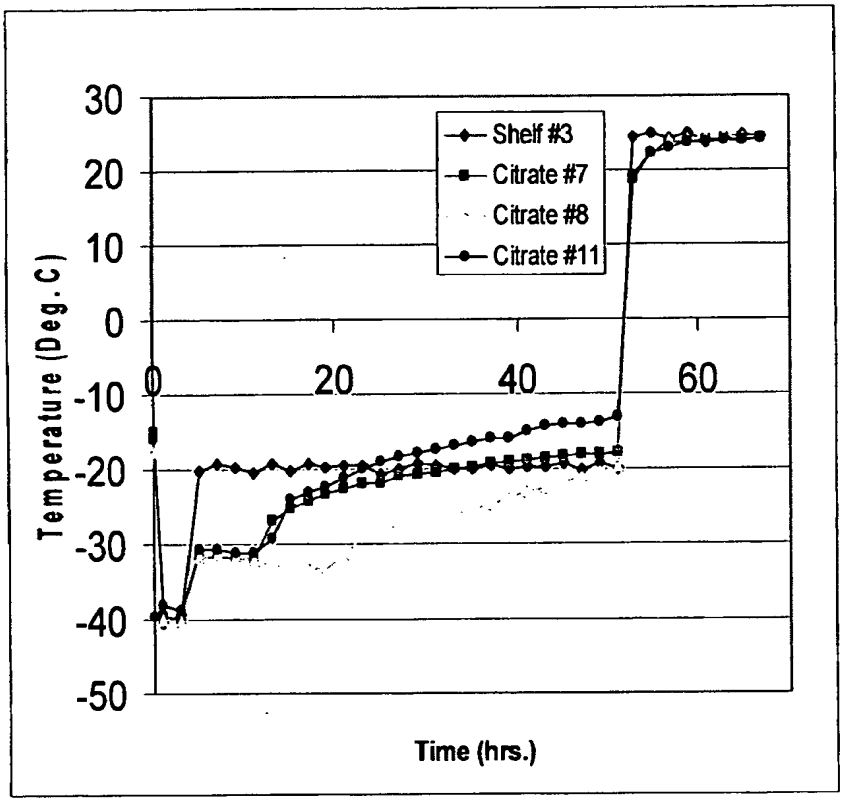

30
20
10
0
-10
-20
-30
-40
-50
0
20
40
60
Temperature (Deg. C)
Time (hrs.)
Shelf #3
Citrate #7
Citrate #8
Citrate #11

Figure 3

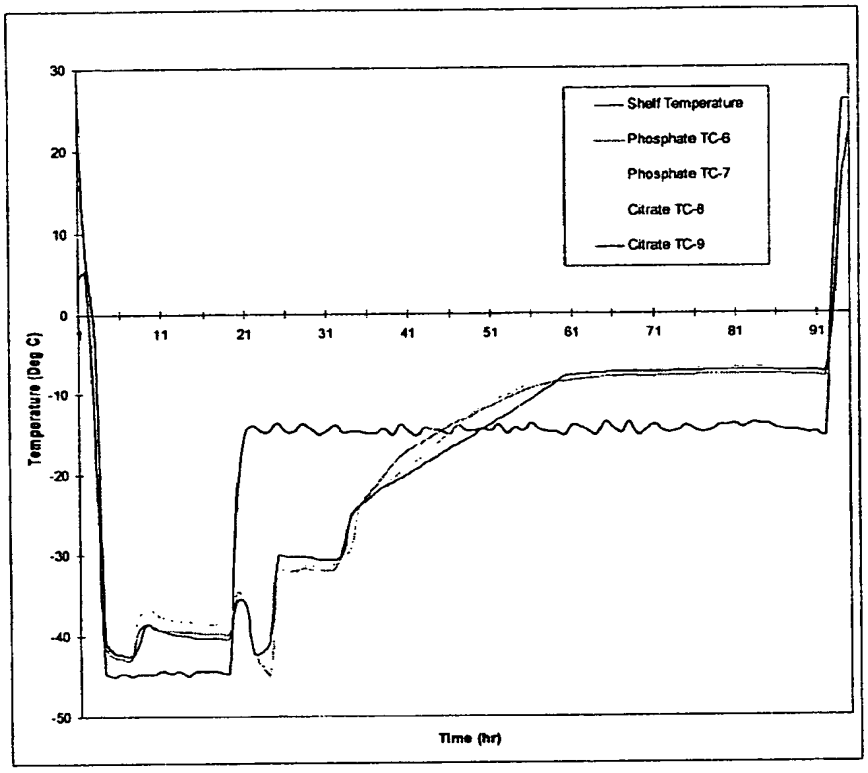

Shelf Temperature
Phosphate TC-6
Phosphate TC-7
Citrate TC-8
Citrate TC-9
Temperature (Deg C)
Time (hr)
30
20
10
0
-10
-20
-30
-40
-50
11
21
31
41
51
61
71
81
91

Figure 4

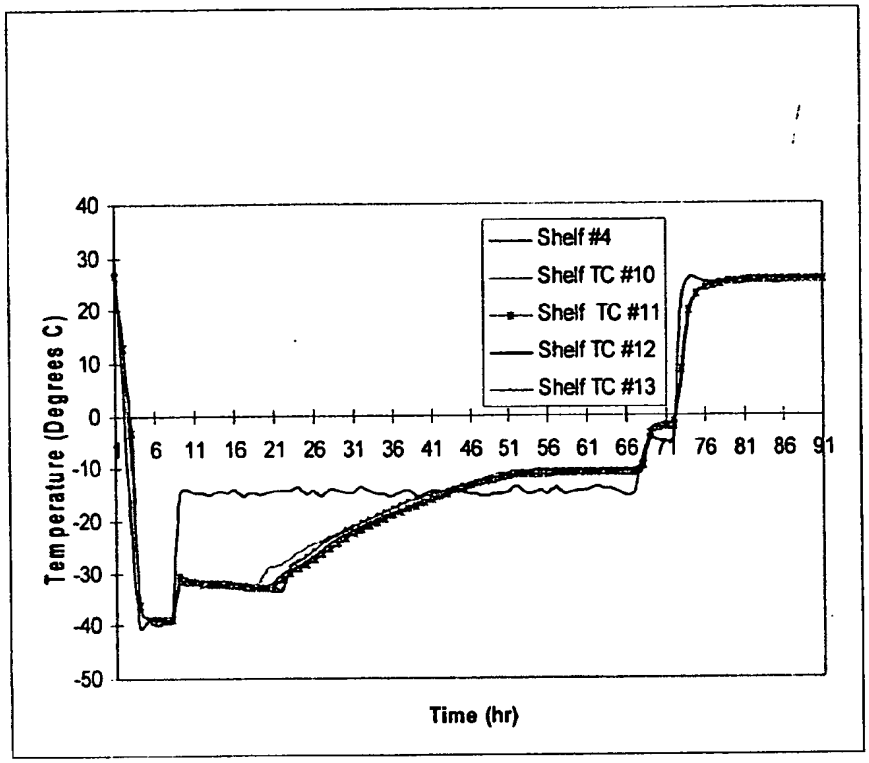
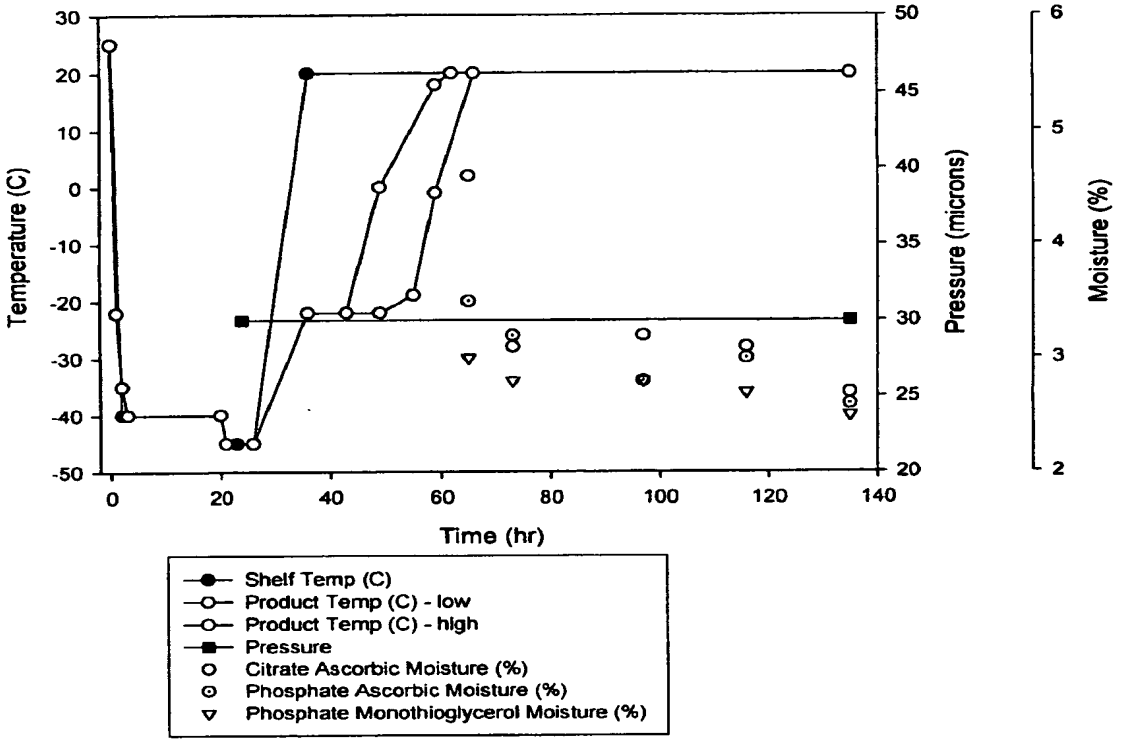

Shelf #4
Shelf TC #10
Shelf TC #11
Shelf TC #12
Shelf TC #13
Temperature (Degrees C)
Time (hr)
40
30
20
10
0
-10
-20
-30
-40
-50
1
6
11
16
21
26
31
36
41
46
51
56
61
66
71
76
81
86
91

Figure 5


Temperature (C)
Pressure (microns)
Moisture (%)
Time (hr)
Shelf Temp (C)
Product Temp (C) - low
Product Temp (C) - high
Pressure
Citrate Ascorbic Moisture (%)
Phosphate Ascorbic Moisture (%)
Phosphate Monothioglycerol Moisture (%)

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13421769	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC- SEARCHED		
Symbol	Date	Examiner
(A61K2300/00 OR A61K38/10 OR A61K31/215 OR A61K8/731 OR C07D213/81 OR C07D213/56).CPC.	9/23/2016	JL

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	9/23/2016	JL
STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	9/23/2016	JL
PALM Inventor Search	9/16/2016	JL
STIC search, results available on SCORE	08/05/2016	JL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/J.L./ Examiner.Art Unit 1676	

PTO/SB/08a (09-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT LIST

(Use as many sheets as necessary)

Complete if Known	
Application Number	13/421,769
Filing Date	March 15, 2012
First Named Inventor	Stephen Comiskey
Art Unit	1676
Examiner Name	Jia-Hai Lee
Attorney Docket Number	SYPA-009/X001US 321994-2142

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code2 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.L/	1.	2015/0366935 A1	12-24-2015	Comiskey et al.	

Examiner Signature:	/JIA-HAI LEE/	Date Considered	09/16/2016

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

(FILE 'HOME' ENTERED AT 10:52:09 ON 23 SEP 2016)

FILE 'REGISTRY' ENTERED AT 10:52:24 ON 23 SEP 2016

L1 77 SEA SPE=ON ABB=ON PLU=ON NDECELCVNVACTGCL/SQSP AND SQL=16

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 10:53:26 ON 23 SEP 2016

L2 83 SEA SPE=ON ABB=ON PLU=ON L1

L3 28663 SEA SPE=ON ABB=ON PLU=ON (MICROCRYSTALLINE CELLULOSE)

L4 0 SEA SPE=ON ABB=ON PLU=ON (LOW MOISTURE CARRIER)

L5 3138319 SEA SPE=ON ABB=ON PLU=ON CHROMATOGRAPHIC OR CHROMATOGRAPHY

L6 722678 SEA SPE=ON ABB=ON PLU=ON TABLET OR CAPSULE OR (BLISTER PACK)

L7 0 SEA SPE=ON ABB=ON PLU=ON L2 AND L3

L8 3 SEA SPE=ON ABB=ON PLU=ON L2 AND L5

L9 14 SEA SPE=ON ABB=ON PLU=ON L2 AND L6

L10 16 SEA SPE=ON ABB=ON PLU=ON L8 OR L9

L11 27 SEA SPE=ON ABB=ON PLU=ON COMISKEY STEPHEN/AU

L12 125 SEA SPE=ON ABB=ON PLU=ON FENG RONG/AU

L13 45 SEA SPE=ON ABB=ON PLU=ON FOSS JOHN/AU

L14 119 SEA SPE=ON ABB=ON PLU=ON SHAILUBHAI KUNWAR/AU

L15 252 SEA SPE=ON ABB=ON PLU=ON L11 OR L12 OR L13 OR L14

L16 19 SEA SPE=ON ABB=ON PLU=ON L15 AND L2

L17 18 DUP REM L16 (1 DUPLICATE REMOVED)

L*** DEL 18 S L15 AND L2

L*** DEL 18 S L15 AND L2

L*** DEL 18 S L15 AND L2

L*** DEL 18 S L15 AND L2

L18 10 SEA SPE=ON ABB=ON PLU=ON L17 AND (AD<2012 OR PD<2012 OR PRD<2012)

L19 16 DUP REM L10 (0 DUPLICATES REMOVED)

L*** DEL 11 S L8 OR L9

L*** DEL 5 S L8 OR L9

L*** DEL 5 S L8 OR L9

L*** DEL 5 S L8 OR L9

L20 7 SEA SPE=ON ABB=ON PLU=ON L19 NOT L16

D L20 1-7 IBIB ABS HITSEQ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Stephen Comiskey *et al*	Confirmation No.:	3135
Application No.:	13/421,769	Group Art Unit:	1676
Filed:	March 15, 2012	Examiner:	LEE, Jia-Hai

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

EFS
Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO FINAL OFFICE ACTION

In response to the Final Office Action mailed October 5th, 2016 please enter the following amendments and remarks. This response is timely filed by January 5th, 2017.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

Amendments to the Claims:

This listing of claims will replace all prior listings in the application. Please amend the claims as follows.

1. (Canceled)

2. (Canceled)

3. (Previously Presented) The oral dosage formulation of claim 45, wherein the GCC agonist peptide has a chromatographic purity of no less than 92% to 95%.

4. (Cancelled)

5. (Currently Amended) The oral dosage formulation of claim 45, wherein the formulation ~~is substantially free of~~ contains less than 0.2% inorganic acids and carboxylic acids.

6. (Canceled)

7. (Canceled)

8. (Previously Presented) The oral dosage formulation of claim 45, wherein the formulation is a solid formulation and the unit dose is a powder, granule, sachet, troche, tablet, or capsule.

9. -19 (Cancelled).

20. (Previously Presented) The oral dosage formulation of claim 45, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

21. (Previously Presented) The oral dosage formulation of claim 45, wherein the formulation is in the form of a capsule or tablet.

22. (Original) The oral dosage formulation of claim 21, wherein the capsule or tablet is in a blister pack or strip.

23. -44. (Canceled)

45. (Previously Presented) An oral dosage formulation consisting of a per unit dose of 3.0 mg or 6.0 mg of a peptide consisting of SEQ ID NO:1, wherein said peptide is a (4,12; 7,15) bicycle, an inert low moisture carrier and a lubricant, wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months.

46. (Previously Presented) The oral dosage formulation of claim 45, wherein the lubricant is magnesium stearate.

47. (Previously Presented) The oral dosage formulation of claim 45, wherein the lubricant is at 0.25% (w/w).

48. (Previously Presented) The oral dosage formulation of claim 45, wherein the inert carrier is microcrystalline cellulose.

49. (Previously Presented) The oral dosage formulation of claim 45, wherein the inert carrier is at least 96% (w/w).

50. (Previously Presented) The oral dosage formulation of claim 45, wherein the inert carrier has a particle size of from 50 to 900 microns.

REMARKS

Status of the Claims

Claims 3, 5, 8, 20-22 and 45-50 are pending. Claim 5 is amended herein. Support for amended claim 5 can be found throughout the application as filed, and specifically for example at paragraph [012]. No new matter has been introduced by this Reply, and thus entry thereof is respectfully requested. The amendments should be entered pursuant to 37 CFR 1.116 as removing rejections and/or narrowing the issues for appeal.

Claims 5 and 45 are not indefinite

The Examiner rejected claims 5 and 45 under 35 USC § 112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. Office Action at page 3. Specifically, the Examiner contends the term "substantially free of" in claim 5 is a relative term which renders the claim indefinite. *Id.* Without acquiescing to the correctness of the Examiner's assertion, to further prosecution, Applicants have herein amended claim 5 to recite the formulation contains less than 0.2% inorganic acids and carboxylic acids.

The Examiner also asserts the term "low moisture carrier" in claim 45 is a relative term which renders the claim indefinite. *Id.* at page 4. Applicants respectfully disagree.

Words of a claim must be given their plain meaning unless such meaning is inconsistent with the specification, and during examination the claims must be interpreted as broadly as their terms reasonably allow. MPEP 2111.01. The determination of claim definiteness must be read in light of the specification and the prosecution history which must inform, with reasonable certainty, those skilled in the art about the scope of the invention. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S.Ct. 2120, 2124 (2014). MPEP § 2173.02 states, in pertinent part,

> "[t]he essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claims is not to be analyzed in a vacuum, but rather in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The person of skill in the art, armed with the knowledge of the art and the teachings of the specification would not find claim 45 indefinite. First, the term "low moisture carrier" would have been known by the skilled artisan to refer to inert carriers that are less hygroscopic than regular carriers. Further, the present application teaches several inert low moisture carriers, for example at paragraphs [044] and [184]. Armed with the teachings in the art and the disclosure of the instant application, the skilled artisan would have been informed about the scope of the invention and would not have found the term "low moisture carrier" in claim 45 to be indefinite.

Accordingly, claims 5 and 45 are not indefinite, and Applicants respectfully request withdrawal of the instant rejections.

The claims are not obvious

The Examiner rejected claims 3, 8, 21, 45-46 and 48 under 35 U.S.C. § 103(a) as allegedly unpatentable over Currie *et al.* (WO 2005/016244; "Currie") in view of FMC biopolymer (2005; "FMC"), Fretzen (US 2010/0048489; "Fretzen"), and Shailubhai (Digestive Disease Week; 2008; "Shailubhai Abstract"). Office Action at pages 5-6. The Examiner argues Currie discloses bicyclic GC-C receptor agonist peptides in formulations that can include binders, lubricants, inert diluents, or microcrystalline cellulose purchased from FMC Corporation. *Id.* at page 6. The Examiner argues FMC shows a range of low moisture Avicel PH grades. *Id.* at page 7. The Examiner contends Fretzen *et al.* teaches an orally administered formulation of a GC-C receptor agonist polypeptide comprising microcrystalline cellulose, and a lubricant. *Id.* at page 8. The Examiner further argues Fretzen *et al.* "shows the chromatographic purity of the GC-C receptor agonist polypeptide decreases by less than 9%....". *Id.* The Examiner states the Shailubhai Abstract teaches a dose range for SP-304 of 2.7mg-5.4mg. *Id.* at page 9. Thus, the Examiner contends the skilled artisan would have been motivated by Fretzen to store Currie's therapeutic in a sealed container containing a desiccant to achieve the chromatographic purity as claimed by Fretzen. *Id.*

The Examiner also rejected claims 45 and 47 under 35 U.S.C. § 103(a) as allegedly

unpatentable over Currie in view of FMC, Fretzen, and the Shailubhai Abstract, and further in view of Chen *et al.* (WO 2007/106468; "Chen"). Office Action at pages 12. The Examiner contends Chen teaches oral table formulation of therapeutic agent comprising a moisture barrier coating, and the tablet contains a lubricant such as magnesium stearate. *Id.* at pages 12-13. The Examiner thus argues it would have been obvious to the skilled artisan to combine the teachings of Currie in view of FMC, Fretzen and the Shailubhai Abstract with Chen's teaching of a lubricant for oral formulation in a tablet is optimized from about 0.1% to about 8% of the total weight of the composition. *Id.* at page 13.

The Examiner also rejected claims 5 and 45 under 35 U.S.C. § 103(a) as allegedly unpatentable over Currie in view of FMC biopolymer, Fretzen, and the Shailubhai Abstract, and further in view of Schaible *et al* (US 2005/014535; "Schaible"). Office Action at page 14. The Examiner contends Schaible teaches a process of producing microcrystalline cellulose, and the skilled artisan would thus have been able to make an oral dosage peptide formulation substantially free of inorganic acids and carboxylic acids to prevent the microcrystalline cellulose from degradation. *Id.*

The Examiner further rejected claims 45 and 49 under 35 U.S.C. § 103(a) as allegedly unpatentable over Currie in view of Yang *et al.* (US 5,817,624; "Yang"), Fretzen, and the Shailubhai Abstract. Office Action at page 15. The Examiner contends that while Currie does not specify mineral oil is an intrinsic inert carrier, Yang shows an oral pharmaceutical formulation comprising a mineral oil which reads on both an inert low moisture carrier and lubricant. *Id.*

Applicants respectfully disagree.

A *prima facie* case of "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). However, the present claims recite the formulation ***consists of*** a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months. This is neither taught nor suggested in the cited art. None of the cited art teaches or suggests a formulation ***consisting*** of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein

the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant where the peptide has a chromatographic purity of no less than 91% after storage for at least three months. For these reasons alone, Applicants assert that the claims are non-obvious over the cited references. This is especially true given the unexpected superior stability of the formulation recited in the amended claims.

Applicants are submitting herein a §1.132 declaration of Dr. Comiskey ("Comiskey Decl.") demonstrating that formulations having a low-moisture inert carrier as recited in the amended claims shows superior results compared with formulations taught in the art, and are more stable than expected compared to formulations comprising a regular-grade carrier. *See* Comiskey Decl. at ¶ 7. Formulations containing a low-moisture carrier demonstrate unexpectedly dramatically decreased amounts of impurities. *See* Comiskey Decl. at ¶ 7-8. These data demonstrate that the formulation required by the claimed methods provides an unexpectedly superior result relative to formulations taught in the art. As noted by Dr. Comiskey, stability of the active ingredient, the peptide of SEQ ID NO: 1, is essential to ensure proper dosing in the treatment of disorders (e.g. chronic constipation or irritable bowel syndrome). *See* Comiskey Decl. at ¶ 9

Furthermore, there is no objective reason provided by the teachings of Currie in view of view of FMC, Fretzen *et al.*, and the Shailubhai Abstract, Yang, Schaible, or Chen would lead the skilled artisan to combine these references, nor is there any evidence that the resultant combination of these references would lead the skilled artisan to arrive at the claimed invention with predictable results. These references, when considered in their entirety, fail to provide the skilled artisan with a reasonable expectation of success.

Currie is cited as teaching bicyclic GC-C receptor agonist peptides in formulations that can include binders, lubricants, inert diluents, or microcrystalline cellulose purchased from FMC Corporation. *See* Office Action in '769 application, pages 6-7. Currie teaches thousands of different GC-C receptor agonist peptides, one of which is the claimed peptide. Currie teaches an equally long list of binders, lubricants, inert diluents, or microcrystalline cellulose, one of which is a low moisture carrier. There is no teaching in Currie that SEQ ID NO:1 is a preferred GC-C receptor agonist. There is therefore no motivation to select SEQ ID NO: 1 in particular from the

list of GC-C receptor agonists. There is no teaching in Currie that an inert low moisture carrier and a lubricant are preferred excipients, and therefore there is no motivation to select those particular excipients from the list of excipients. Furthermore, there is certainly no motivation to select SEQ ID NO:1, an inert low moisture carrier, and a lubricant for use in a pharmaceutical composition, let alone a pharmaceutical composition having a per unit dose of 3 mg or 6 mg as required by the claims. Accordingly, the teachings of Currie fail to establish a *prima facie* case of obviousness against the current claims.

Given the fatal deficiency of Currie, one of ordinary skill would have had no motivation to combine the teachings of Currie with FMC, Fretzen, and the Shailubhai Abstract, Yang, Schaible, or Chen either alone or in combination to reach the claimed invention with a reasonable expectation of success. The mere fact that something is possible does not, standing alone, support an obviousness rejection. Rather, an objective reason to combine the references is required. *See* MPEP § 2143.01 (IV). Here, the Examiner has not provided the required articulated reasoning and, in fact, nothing in the cited art provides any reason to arrive at the formulation recited claim 1. The Examiner has therefore failed to make a *prima facie* case of obviousness.

FMC merely discloses a range of low moisture Avicel PH grades. Chen merely discloses tablets containing magnesium stearate as the lubricant. Schaible merely teaches a process of producing microcrystalline cellulose. Yang merely teaches an oral pharmaceutical formulation comprising a mineral oil.

Fretzen is cited as teaching GC-C receptor agonist formulations with the claimed chromatographic purity. Specifically, the Examiner points to the chromatographic purity of the formulations disclosed in Table 7 of Fretzen. However, as shown in the table below, none of these formulations ***consist*** of a GC-C receptor agonist peptide an inert low moisture carrier and a lubricant.

Example	**Formulation Components**	**% Linaclotide (taken from Table 7 of Fretzen)**
1	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***99.13***

3	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***99.42***
4	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***97.83***
5	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***98.68***
6	$MgCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	95.51
7	ZnAc, leucine, hypromellose, linaclotide, celphere CP-305	95.36
8	Leucine, hypromellose, linaclotide, celphere CP-305	94.90
9	$CaCl_2$, hypromellose, linaclotide, celphere CP-305	96.55
10	hypromellose, linaclotide, celphere CP-305	**87.77**
11	hypromellose, linaclotide, celphere CP-305	**91.63**
12	$CuCl_2$, hypromellose, linaclotide, celphere CP-305	**43.15**
13	ZnAc, hypromellose, linaclotide, celphere CP-305	94.01
14	$MgCl_2$, hypromellose, linaclotide, celphere CP-305	92.70
15	Methionine, hypromellose, linaclotide, celphere CP-305	93.24
17	$CaCl_2$, hypromellose, linaclotide, celphere CP-305	95.16

Moreover, all of the formulations disclosed in Fretzen contain components in addition to a GC-C receptor agonist, an inert low moisture carrier, and a lubricant. Importantly, as shown in the table above, the most stable formulations (e.g. those from examples 1, 3, 4, and 5) all contain $CaCl_2$ and leucine, while the least stable (e.g. those from examples 10, 11, and 12) all lack an amino acid and/or a cation. Given the chromatographic purities demonstrated by the formulations disclosed in Fretzen, the skilled artisan would not have been motivated to alter the Fretzen formulations to remove components. Moreover, the skilled artisan would not have done so with a reasonable expectation of success of obtaining the claimed chromatographic purity.

Finally and of critical importance, Fretzen fails to disclose any formulation with the claimed GC-C receptor agonist peptide. There are three different families of GC-C receptor agonist peptides— Uroguanylin, Guanylin and heat-stable enterotoxin. Although, each of these family of peptide share the common function of binding the GC-C receptor they all have different physiological purposes.

Uroguanylin is secreted by enterochromaffin cells in the duodenum and proximal small

intestine. Uroguanylin acts as an agonist of the guanylyl cyclase receptor GC-C and regulates electrolyte and water transport in intestinal and renal epithelia. Guanylin is secreted by goblet cells in the colon and induces chloride secretion and decreases intestinal fluid absorption. Both uroguanylin and guanylin are *endogenous* peptide hormones that physiologically regulate R-GC signaling proteins in target cells. In contrast, heat-stable enterotoxins are *bacterial* enterotoxins, which have greater potency than the endogenous peptides, and induce excessive fluid secretion into intestinal lumen leading to secretory diarrhea (i.e., Travellers' Diarrhea)

The claimed peptide is structurally related to the endogenous hormone uroguanylin. In contrast, the Fretzen peptides are structurally related to *bacterial* heat-stable enterotoxin. Thus one skilled in the art would not have been motivated to alter the Fretzen formulations to replace a bacterially derived peptide with a endogenous human derived peptides. Moreover, the skilled artisan would not have done so with a reasonable expectation of success of obtaining the claimed chromatographic purity.

Further, as explained above, Applicants have surprisingly discovered that formulations consisting of just a uroguanylin derived GC-C receptor agonist, an inert low moisture carrier, and a lubricant show superior results compared with formulations taught in the art, and are more stable than expected compared to formulations comprising a regular-grade carrier. *See* Comiskey Decl. at ¶ 7.

The cited art therefore does not provide a suggestion of all elements of the pending claims. Nor does it teach or predict the surprising stability demonstrated by the instantly claimed formulations. Accordingly the claimed formulations are not obvious, and Applicants respectfully request withdrawal of the instant rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees, including those under 37 C.F.R. §§1.16, 1.17, and 1.21, that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: January 5, 2017

Respectfully submitted,
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140268585 v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Stephen Comiskey *et al.*	Confirmation No.:	3139
Application No.:	13/421,769	Group Art Unit:	1676
Filed:	March 15, 2012	Examiner:	LEE, Jae-Hee

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

U.S. Patent and Trademark Office
Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, the undersigned Stephen Comiskey, declare and as follows:

1. I am Principal Scientist at Synergy Pharmaceutical, the assignee of the above referenced patent application. I received my B.S. in Biochemistry, M.S. in Food Chemistry, and Ph.D. in Pharmaceutics from the University of Wisconsin-Madison.

2. I understand that the present claims are directed to directed to formulations consisting of a per unit dose of 3 mg or 6 mg of SP-304 (SEQ ID NO: 1), an inert low moisture carrier, and a lubricant, and wherein the SP-304 in the composition has a chromatographic purity of no less than 91% after storage for at least three months.

3. I have reviewed the Office Action mailed October 5, 2016. I understand that the pending claims are rejected under 35 U.S.C. 103(a) as allegedly being obvious in several rejections:

- Claims 3, 8, 21, 45-46 and 48 are rejected over Currie *et al.* (WO 2005/016244; "Currie") in view of FMC biopolymer (2005; "FMC"), Fretzen (US 2010/0048489;

Fretzen, and Shailubhai (Digestive Disease Week, 2008; "Shailubhai Abstract") (Office Action at pages 5-6;

- Claims 45 and 47 over Currie *et al.* in view of FMC, Fretzen, and the Shailubhai Abstract, and further in view of Chen *et al.* (WO 2007/106468; "Chen"). *Id.* at pages 13;
- Claims 5 and 45 over Currie in view of FMC biopolymer, Fretzen, and Shailubhai, and further in view of Schaible *et al.* (US 2005/014535; "Schaible"). *Id.* at page 14; and
- Claims 45 and 49 over Currie in view of Yang *et al.* (US 5,817,624; "Yang"), Fretzen, and Shailubhai. *Id.* at page 15.

4. I make this declaration to rebut the Examiner's rejection, with which I do not agree.

5. At the time of filing, those working in the field would not have found the presently formulation recited in the claims obvious based on the teachings in the cited art. It is my opinion that the claimed methods are not obvious over the above cited references, for at least the following reasons.

6. We conducted studies to test the stability and purity of various formulations comprising the peptide of SEQ ID NO:1 (SP-304) and discovered that a low-moisture carrier improved the stability of a GCC agonist peptide compared to a regular grade carrier.

7. Appendix A shows total impurities and impurities relative to the retention of time (RRT) at both 25°C and 40°C in formulations of GCC agonist peptides comprising the low-moisture carrier (Avicel PH112) compared with the regular grade carrier (Avicel PH102). Formulations of plecanatide (a GCC agonist peptide of SEQ ID NO: 1) tablet with low-moisture Avicel PH112 shows improved stability compared to regular grade Avicel.

8. This reduction in total impurities and impurities relative to the retention of time (RRT) with the low-moisture carrier (Avicel PH112) is surprising. Other than the low-moisture

element of Avicel PH112, the two carriers are the same, but the reduced moisture content of the low-moisture carrier (~1.5%)[1] had a greater effect on protein stability than expected. As shown in Appendix A, a 1.5% reduction in the water content resulted in approximately a 37% decrease in total impurities at 9 months at 25°C (2.733±0.289 for Avicel PH102; 1.7±0.00 for Avicel PH112) and approximately a 29% decrease in total impurities at 9 months at 40°C (4.767±0.322 for Avicel PH102; 3.36±0.207 for Avicel PH112). This dramatic reduction in impurities was surprising unexpected.

9. In my opinion the superior stability of the formulation as required by the claims is not without consequence. As without stability of the active ingredient (i.e., the peptide of SEQ ID NO:1) accurate dosing to treat disorders (e.g. chronic constipation or irritable bowel syndrome) could not be accomplished.

10. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

S. Comiskey
Stephen Comiskey
Signed, January 5, 2017

[1] http://www.fmcbiopolymer.com/Portals/bio/content/Docs/PS-Section%2011.pdf, at page 9

[illegible]

APPENDIX A

Improved Plecanatide Tablet Stability (reduced impurity levels) using low moisture Avicel PH112 compared to regular Avicel PH102

Created July 10, 2014

		Sum of Total Impurities (Area%)												
		25C								40C				
Batch (dosage form)	Months→ Avicel↓	0	1	2	3	6	9	12	18	0	1	2	3	6
2011F100A (3mg capsule)	PH102	2.4	2.6	2.6	2.9	2.9	2.9	3.2	3.3	2.4	3.2	3.6	4.2	4.9
11H140 (3mg capsule)	PH102	2.1	2.5	2.7	2.6	2.8	2.9	3.4	3.6	2.1	3.5	3.6	4.0	5.0
12G080 (3mg tablet)	PH102	1.9	2.7	2.2	2.3	2.4	2.4	2.7		1.9	3.0	2.8	3.2	4.4
13C049 (3mg tablet)	PH112	1.2	1.2	1.4	1.4	1.7	1.7			1.2	1.7	2.1	3.1	3.2
13C050 (3mg tablet)	PH112	1.2	1.2	1.3	1.4	1.7	1.7			1.2	1.7	2.1	2.3	3.4
13C051 (6mg tablet)	PH112	1.1	1.2	1.3	1.4	1.5	1.7			1.1	1.7	2.5	2.2	3.2
13E090 (3mg tablet)	PH112	1.3	1.2	1.2	1.4	1.6				1.3	1.8	2.5	2.6	3.3
13F106 (6mg tablet)	PH112	1.7	1.6	1.5	1.9	2.1				1.7	1.9	2.6	2.8	3.7

		Impurity RRT 0.97 (Area%)												
		25C								40C				
Batch (dosage form)	Months→ Avicel↓	0	1	2	3	6	9	12	18	0	1	2	3	6
2011F100A (3mg capsule)	PH102	0.48	0.26	0.34	0.00	0.43	0.33	0.38	0.20	0.48	0.29	0.31	0.31	0.33
11H140 (3mg capsule)	PH102	0.11	0.20	0.26	0.00	0.31	0.36	0.63	0.15	0.11	0.22	0.25	0.24	0.25
12G080 (3mg tablet)	PH102	0.00	0.30	0.00	0.30	0.00	0.00	0.00		0.00	0.34	0.00	0.00	0.00
13C049 (3mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00	0.00			0.00	0.00	0.00	0.00	0.00
13C050 (3mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00	0.00			0.00	0.00	0.00	0.00	0.00
13C051 (6mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00				0.00	0.00	0.00	0.00	0.00
13E090 (3mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00				0.00	0.00	0.00	0.00	0.00

13F100 (5mg tablet)	PH112	0.00	0.12	0.00	0.15	0.19				0.00	0.00	0.18	0.00	0.12

		Impurity RRT 1.33 (Area%)												
		25C								40C				
Batch (dosage form)	Months→ Avicel↓	0	1	2	3	6	9	12	18	0	1	2	3	6
2011F100A (3mg capsule)	PH102	0.29	0.49	0.54		0.69	0.92	1.10	1.32	0.29	1.00	1.36	1.73	2.49
11H140 (3mg capsule)	PH102	0.31	0.45	0.54	0.60	0.79	0.95	1.04	1.48	0.31	1.10	1.48	1.84	2.77
12C080 (3mg tablet)	PH102	0.12	0.21	0.29	0.34	0.50	0.57	0.61		0.12	0.54	0.83	0.97	1.53
13C049 (3mg tablet)	PH112	0.22	0.29	0.36	0.38	0.56	0.58			0.22	0.65	0.82	1.54	1.45
13C050 (3mg tablet)	PH112	0.21	0.32	0.33	0.39	0.54	0.58			0.21	0.62	0.84	0.95	1.42
13C051 (6mg tablet)	PH112	0.22	0.26	0.35	0.38	0.50				0.22	0.66	1.15	0.90	1.39
13E080 (3mg tablet)	PH112	0.25	0.31	0.37	0.43	0.51				0.25	0.65	0.94	1.11	1.43
13F100 (5mg tablet)	PH112	0.20	0.25	0.29	0.43	0.47				0.20	0.59	0.76	1.03	1.38

Electronic Acknowledgement Receipt

EFS ID:	27982103
Application Number:	13421769
International Application Number:	
Confirmation Number:	3135
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009X01US 321994-2142
Receipt Date:	05-JAN-2017
Filing Date:	15-MAR-2012
Time Stamp:	18:40:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1SYPA-009-X01US_321994-2142_ResponseToFOA_AsFiled.pdf	185240 9e71da2e06fcc3570819e0c1ec0c6e53603e20ad	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	11

Warnings:					
Information:					
2	Oath or Declaration filed	1SYPA-009-X01US_321994-2142_Declaration_AsFiled.pdf	1628039 b2a8b570461d5007671755b0bcda9b4ec9b11e03	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	1813279		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/421,769	Filing Date 03/15/2012	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **01/05/2017**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 12	Minus	** 44	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
JAMES TUNSTALL

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

58249 7590 02/24/2017

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER
LEE, JIA-HAI

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 02/24/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142	3135

TITLE OF INVENTION: Formulations of Guanylate Cyclase C Agonists and Methods of Use

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/24/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 02/24/2017
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142	3135

TITLE OF INVENTION: Formulations of Guanylate Cyclase C Agonists and Methods of Use

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/24/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, JIA-HAI	1676	424-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

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13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142	3135

58249 7590 02/24/2017

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1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
LEE, JIA-HAI	

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 02/24/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/421,769	Applicant(s) COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *01/05/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *3,5,8,20-22 and 45-50*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20170215* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☒ Other *ANE.I and IMIS*.

/SATYANARAYANA R GUDIBANDE/
Primary Examiner, Art Unit 1676

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

The Finality of the prior office action dated 10/05/2016 is withdrawn to place the instant claims in condition for allowance.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Ms. Anne E. Fleckenstein on 2/15/2017.

The application has been amended as follows:

In claim 45, at line 1, insert --"of a Guanylate Cyclase-C (GCC) agonist peptide"-- after the word "formulation".

Reasons for allowance

The following is an examiner's statement of reasons for allowance:

The closest prior art Currie et al. (WO 2005/016244 A2) taught a GC-C receptor agonist peptide formula in claim 6 reads on the instant SEQ ID NO: 1. Currie et al. also taught a composition comprising the peptide and one or more inert excipients including

microcrystalline cellulose, diluents, lubricants, binders, and disintegrating agents, but the reference did not disclose a composition consisting of 3 mg or 6 mg of a [4,12; 7,15] bicycle peptide consisting of SEQ ID NO: 1, an inert low moisture carrier, and a lubricant having a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

Another closest prior art reference Shailubhai et al. (Digestive Disease Week. San Diego, 2008) disclosed the identical peptide sequence of SEQ ID NO: 1 named SP-304 can be optimized between 2.7 mg and 8.4 mg but the reference did not disclosed an inert low moisture carrier, and a lubricant having a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

Applicant's amendment to claim 45 limits the oral dosage composition to be consisting of 3 mg or 6 mg of a [4,12; 7,15] bicycle peptide consisting of SEQ ID NO: 1, an inert low moisture carrier, and a lubricant having a chromatographic purity of no less than 91 % after storage for at least three months to differentiate this instant invention from the prior art teachings; therefore, this instant invention is allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached on Mon-Fri from 9:00 A.M. to 5:30 P.M..

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on 571-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./
Examiner, Art Unit 1676

21-February-2017

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/421,769	COMISKEY ET AL.	
	Examiner	Art Unit	
	JIA-HAI LEE	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JIA-HAI LEE*. (3)_____.

(2) *Anne E. Fleckenstein*. (4)_____.

Date of Interview: *15 February 2017*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *45*.

Identification of prior art discussed: *N/A*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The argeement was reached. Applicant's representative authorized the examiner to add the phrase "of guanylate cyclase-C (GCC) agonist peptide" in line 1 of claim 45 to place the claims in condition for allowance..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/J. L./ Examiner, Art Unit 1676	

(FILE 'HOME' ENTERED AT 13:45:01 ON 15 FEB 2017)

FILE 'REGISTRY' ENTERED AT 13:45:09 ON 15 FEB 2017

L1 80 SEA SPE=ON ABB=ON PLU=ON NDECELCVNVACTGCL/SQSP AND SQL=16

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 13:45:38 ON 15 FEB 2017

L2 29511 SEA SPE=ON ABB=ON PLU=ON (MICROCRYSTALLINE CELLULOSE) OR (LOW MOISTURE CARRIER)

L3 207173 SEA SPE=ON ABB=ON PLU=ON LUBRICANT OR (MAGNESIUM STEARATE)

L4 93 SEA SPE=ON ABB=ON PLU=ON L1

L5 0 SEA SPE=ON ABB=ON PLU=ON L2 AND L3 AND L4

L6 3171895 SEA SPE=ON ABB=ON PLU=ON CHROMATOGRAPHIC OR CHROMATOGRAPHY

L7 3 SEA SPE=ON ABB=ON PLU=ON L4 AND L6

L8 0 SEA SPE=ON ABB=ON PLU=ON L4 AND L2

L9 27 SEA SPE=ON ABB=ON PLU=ON COMISKEY STEPHEN/AU

L10 129 SEA SPE=ON ABB=ON PLU=ON FENG RONG/AU

L11 45 SEA SPE=ON ABB=ON PLU=ON FOSS JOHN/AU

L12 126 SEA SPE=ON ABB=ON PLU=ON SHAILUBHAI KUNWAR/AU

L13 263 SEA SPE=ON ABB=ON PLU=ON L9 OR L10 OR L11 OR L12

L14 22 SEA SPE=ON ABB=ON PLU=ON L13 AND L4

L15 0 SEA SPE=ON ABB=ON PLU=ON L14 AND L2

L16 0 SEA SPE=ON ABB=ON PLU=ON L15 AND (AD<2011 OR PD<2011 OR PRD<2011)

L17 23 SEA SPE=ON ABB=ON PLU=ON L7 OR L14

L18 22 DUP REM L17 (1 DUPLICATE REMOVED)

D L18 1-22 IBIB ABS HITIND

OK TO ENTER: /J.L/ Claim 45 is subject to examiner's amendment.

Amendments to the Claims:

This listing of claims will replace all prior listings in the application. Please amend the claims as follows.

1. (Canceled)

2. (Canceled)

3. (Previously Presented) The oral dosage formulation of claim 45, wherein the GCC agonist peptide has a chromatographic purity of no less than 92% to 95%.

4. (Cancelled)

5. (Currently Amended) The oral dosage formulation of claim 45, wherein the formulation ~~is substantially free of~~ contains less than 0.2% inorganic acids and carboxylic acids.

6. (Canceled)

7. (Canceled)

8. (Previously Presented) The oral dosage formulation of claim 45, wherein the formulation is a solid formulation and the unit dose is a powder, granule, sachet, troche, tablet, or capsule.

9. -19 (Cancelled).

20. (Previously Presented) The oral dosage formulation of claim 45, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

21. (Previously Presented) The oral dosage formulation of claim 45, wherein the formulation is in the form of a capsule or tablet.

22. (Original) The oral dosage formulation of claim 21, wherein the capsule or tablet is in a blister pack or strip.

23. -44. (Canceled)

45. (Previously Presented) An oral dosage formulation consisting of a per unit dose of 3.0 mg or 6.0 mg of a peptide consisting of SEQ ID NO:1, wherein said peptide is a (4,12; 7,15) bicycle, an inert low moisture carrier and a lubricant, wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months.

46. (Previously Presented) The oral dosage formulation of claim 45, wherein the lubricant is magnesium stearate.

47. (Previously Presented) The oral dosage formulation of claim 45, wherein the lubricant is at 0.25% (w/w).

48. (Previously Presented) The oral dosage formulation of claim 45, wherein the inert carrier is microcrystalline cellulose.

49. (Previously Presented) The oral dosage formulation of claim 45, wherein the inert carrier is at least 96% (w/w).

50. (Previously Presented) The oral dosage formulation of claim 45, wherein the inert carrier has a particle size of from 50 to 900 microns.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Stephen Comiskey *et al*	Confirmation No.:	3135
Application No.:	13/421,769	Group Art Unit:	1676
Filed:	March 15, 2012	Examiner:	LEE, Jia-Hai

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

EFS
Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

OK TO ENTER: /J.L/
02/15/2017

RESPONSE TO FINAL OFFICE ACTION

In response to the Final Office Action mailed October 5th, 2016 please enter the following amendments and remarks. This response is timely filed by January 5th, 2017.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13421769	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

CPC								
Symbol							**Type**	**Version**
A61K		38	/	10			F	2013-01-01
A61K		38	/	12			I	2013-01-01
C07K		7	/	08			A	2013-01-01
C07K		7	/	64			A	2013-01-01
A61K		9	/	1623			I	2013-01-01
A61K		9	/	1652			I	2013-01-01
A61K		9	/	1676			I	2013-01-01
A61K		9	/	2054			I	2013-01-01
A61K		9	/	4858			I	2013-01-01
A61K		9	/	4866			I	2013-01-01
A61K		45	/	06			I	2013-01-01
			/					
			/					
			/					
			/					

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		38	/	10	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01

/J.L./ Examiner.Art Unit 1676 (Assistant Examiner)	02/15/2017 (Date)	**Total Claims Allowed:** 12	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676 (Primary Examiner)	02/21/2017 (Date)	O.G. Print Claim(s) 45	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13421769	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
424	451	A	6	1	K	38 / 10 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

/J.L./ Examiner.Art Unit 1676	02/15/2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	02/21/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	45	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13421769	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
2	3														
3	5														
4	8														
5	20														
6	21														
7	22														
1	45														
8	46														
9	47														
10	48														
11	49														
12	50														

/J.L./ Examiner.Art Unit 1676	02/15/2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	02/21/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	45	none

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	14	NDECELCVNVACTGCL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L2	709	(guanylate near cyclase near C)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L3	13	inert with low with moisture with carrier	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L4	278992	magnesium with stearate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L5	141574	microcrystalline with cellulose	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L6	13	L1 and L4 and L5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L7	121	(Stephen near3 Comiskey).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L8	290	(Rong near3 Feng).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L9	138	(John near3 Foss).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L10	236	(Kunwar near3 Shailubhai).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L11	691	L7 or L8 or L9 or L10	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L12	151	L2 and L4 and L5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L13	27	L12 and @py<"2011"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L14	22	L13 not L6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L15	56	L11 and L2 and L4 and L5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L16	50	L15 not L14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	WITH	ON	2017/02/15 15:50

			DERWENT; IBM_TDB			
L17	0	L16 and @py<"2011"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L18	52	(SYNERGY near3 PHARMACEUTICALS).asn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L19	0	L18 and L1	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L20	31	L18 and L2 and L4 and L5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50
L21	6	L20 and @py<"2011"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/02/15 15:50

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L22	14	NDECELCVNVACTGCL	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:51
L23	400	(guanylate near cyclase near C)	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:51
L24	235080	magnesium with stearate	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:51
L25	113550	microcrystalline with cellulose	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:51
L26	149	L23 and L24 and L25	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:52
L27	32	L26 and (chromatographic with purity)	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:53
L28	22	(Stephen near3 Comiskey).in.	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:54
L29	74	(Rong near3 Feng).in.	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:54
L30	41	(John near3 Foss).in.	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:55
L31	67	(Kunwar near3 Shailubhai).in.	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:55
L32	192	L28 or L29 or L30 or L31	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:56
L33	38	(SYNERGY near3 PHARMACEUTICALS).asn.	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:56
L35	56	L32 and L23 and L24 and L25	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:58
L36	4	L35 and L27	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:58
L37	38	(SYNERGY near3 PHARMACEUTICALS).asn.	US-PGPUB; USPAT	WITH	ON	2017/02/15 15:59
L38	31	L37 and L26	US-PGPUB; USPAT	WITH	ON	2017/02/15 16:00

2/15/2017 4:02:25 PM

C:\ Users\ jlee24\ Documents\ EAST\ Workspaces\ 13421769-allow.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13421769	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	2/15/2017	JL
STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	2/15/2017	JL
PALM Inventor Search	2/15/2017	JL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	EAST, Database: USPATFUL, USPGPUB	2/15/2017	JL
	STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	2/15/2017	JL
	PALM Inventor Search	2/15/2017	JL

/J.L./ Examiner.Art Unit 1676	

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 02/24/2017
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142	3135

TITLE OF INVENTION: Formulations of Guanylate Cyclase C Agonists and Methods of Use

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/24/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, JIA-HAI	1676	424-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Cynthia A. Kozakiewicz
2 Ivor Elrifi
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SYNERGY PHARMACEUTICALS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): NEW YORK, NEW YORK

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ● Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ● Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ● The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-1283 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Anne E. Fleckenstein/ Date March 1, 2017

Typed or printed name Anne E. Fleckenstein Registration No. 62,951

Electronic Patent Application Fee Transmittal

Application Number:	13421769
Filing Date:	15-Mar-2012
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Filer:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009X01US 321994-2142

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	28499452
Application Number:	13421769
International Application Number:	
Confirmation Number:	3135
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009X01US 321994-2142
Receipt Date:	01-MAR-2017
Filing Date:	15-MAR-2012
Time Stamp:	14:02:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$480
RAM confirmation Number	030217INTEFSW00000291501283
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	SYPA_009_X01US_IssueFeeTransmittal.pdf	357432 639af3f328554d70e00e3de09c840d29f489c657	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30516 ca7d1408949abb5071af7be9e04c40a80a3b2492	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	387948		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Notice of References Cited	Application/Control No. 13/421,769	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2005/0145351 A1	07-2005	Schaible, David	C08B15/02	162/9
*	B	US-5,817,624 A	10-1998	Yang; Heechung	A61K9/4858	514/11.4
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO2007106468A2	09-2007	~~US~~ WO	Chen et al.	
	O	Change(s) applied				
	P	to document,				
	Q	/M.H./				
	R	3/2/2017				
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 13/421,769	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 2005/016244 A2	02-2005	~~US~~ WO	Currie	A61K
	O	Change(s) applied				
	P	to document,				
	Q	/M.H./				
	R	3/2/2017				
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Mihranyan et al. Moisture sorption by cellulose powders of varying crystallinity. Int J Pharm. 2004 Jan 28;269(2):433-42.
	V	Lai et al. Solid-State Chemical Stability of Proteins and Peptides. J Pharm Sci. 1999 May;88(5):489-500. Review.
	W	FMC biopolymer of Avice PH production instruction (2005).
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 13/421,769	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2009/0253634	10-2009	Currie et al.	514/14
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 2010/027404 A2	03-2010	~~US~~ WO	Fretzen et al.	A61K38/17, A61K9/14
	O	WO 02/078683 A1	10-2002	~~US~~ WO	Shailubhai et al.	A61K31/00, C07K2/00
	P	Change(s) applied				
	Q	to document,				
	R	/M.H./				
	S	3/2/2017				
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/SB/08a (09-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT LIST

(Use as many sheets as necessary)

Complete if Known	
Application Number	13/421,769
Filing Date	March 15, 2012
First Named Inventor	Stephen Comiskey
Art Unit	1676
Examiner Name	Jia-Hai Lee
Attorney Docket Number	SYPA-009/X001US 321994-2142

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code2 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	21.	2010/0093635 A1	04-15-2010	Shailubhai	
	22.	2010/0120694 A1	05-13-2010	Shailubhai et al.	
	23.	2010/0152118 A1	06-17-2010	Shailubhai	
	24.	2010/0221329 A1	09-02-2010	Shailubhai et al.	
	25.	2012/0196797 A1	08-02-2012	Currie et al.	
	26.	2012/0237593 A1	09-20-2012	Comiskey et al.	
	27.	2012/0289460 A1	11-15-2012	Shailubhai	
	28.	2013/0274204 A1	10-17-2013	Shailubhai et al.	
	29.	2014/0024605 A1	01-23-2014	Shailubhai et al.	
	30.	2014/0121169 A1	05-01-2014	Shailubhai et al.	
	31.	2014/0135274 A1	05-15-2014	Shailubhai	
	32.	2014/0287002 A1	09-25-2014	Shailubhai	
	33.	2014/0329738 A1	11-06-2014	Shailubhai et al.	
	34.	5,106,834	04-21-1992	Bovy et al.	
	35.	5,130,333	07-14-1992	Pan et al.	
Change(s) applied to document, /K.D./ 3/3/2017	36.	5,489,670 02/1996	~~02-06-1994~~	Currie et al.	
	37.	5,518,888	05-21-1996	Waldman et al.	
	38.	5,578,709	11-26-1996	Woiszwillo et al.	
	39.	5,601,990	02-11-1997	Waldman et al.	
	40.	5,731,159	03-24-1998	Waldman et al.	

Examiner Signature:		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/421,769	04/11/2017	9616097	SYPA-009X01US 321994-2142	3135

58249 7590 03/22/2017

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 291 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Stephen Comiskey, Doylestown, PA;
Rong Feng, Langhorne, PA;
John Foss, Doylestown, PA;
Kunwar Shailubhai, Audubon, PA;

Attorney Docket No. SYPA-009X01US 321994-2142 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Stephen Comiskey et al.	Confirmation No.:	3135
Application No.:	13/421,769	Group Art Unit:	1676
Filed:	March 15, 2012	Examiner:	Jia-Hai LEE

FOR: Formulations of Guanylate Cyclase C Agonists and Methods of Use

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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR RECONSIDERATION OF PATENT TERM INDICATED ON FACE OF PATENT UNDER 37 C.F.R. § 1.705(b)

U.S. Patent No. 9,616,097 issued April 11, 2017 from the above referenced application. The face of the patent indicates that the patent term adjustment is **291** days. Applicants hereby respectfully request reconsideration of the patent term adjustment. Specifically, Applicants believe that the total patent term adjustment should be **340** days.

In support of this request, Applicants submit the following statement of facts pursuant to 37 C.F.R. § 1.705(b).

(i) The United States Patent and Trademark Office ("Office") calculated the adjustment under 35 U.S.C. § 154(b)(1)(A) as **383** days (USPTO A Delay). Applicants do not dispute this number.

(ii) The Office calculated the adjustment under 35 U.S.C. § 154(b)(1)(B) due to the failure of the Office to issue a patent within three years after the date on which the application was filed as **295** days (USPTO B Delay). Applicants do not dispute this number.

(iii) The Office calculated the adjustment under 35 U.S.C. § 154(b)(1)(C) as **0** days (USPTO C Delay). Applicants do not dispute this number.

(iv) The Office calculated the adjustment under 35 U.S.C. § 154(b)(2)(A), for the overlapping days between {A and B} or {A and C} as **0** days. Applicants do not dispute this number.

(v) The correct adjustment calculated under 35 U.S.C. § 154(b)(2)(C) for Applicants' failure to engage in reasonable efforts to conclude prosecution of the application is **338** days (not 387 days as calculated by the Office). This number differs from that calculated by the Office by **49** days.

Applicants believe that the Office incorrectly attributed 71 days of delay to Applicants under 37 CFR § 1.704(c)(8). Specifically, the Supplemental Response filed September 14, 2016 ("the Supplemental Response") was submitted at the express request of the Examiner in reply to the Examiner Initiated Interview held on September 14, 2016. Applicants included an Interview Summary in the Supplemental Response stating, "Provided below is a summary of the telephonic Interview held on September 14, 2016. The participants in the interview were Jia-Hai Lee (Examiner), Karlheinz R. Skowronek (Examiner Lee's Supervisor),Cynthia Kozakiewicz (Attorney, Cooley LLP), and Ivor Elrifi (Attorney, Cooley LLP). During the interview, the Examiner requested that the claims in the instant application be amended to the same scope as the formulation recited in the method of use claims in co-pending application 14/845,644. Applicants submit this Supplemental Amendment and Response, according to the Examiner's express request."

Accordingly, because the Supplemental Response was filed at the express request of the Examiner, Applicants submit that it should not have incurred any days of Applicant delay under 35 U.S.C. §1.704(c)(8).

However, the Information Disclosure Statement filed on July 27, 2016 should have incurred Applicant delay under 37 CFR § 1.704(c)(8) for the period from July 6, 2017 (the day after the Response to Non-Final Rejection was filed) until July 27, 2016 (the date the Information Disclosure Statement was filed) for a total of 22 days.

Thus, the total number of days of delay attributable to Applicants under 37 C.F.R. § 1.704 should be **338** (92+92+40+92+22) days.

(vi) Accordingly, the total patent term adjustment for this patent should be **340** days (383 days of A delay + 295 days of B delay + 0 days of C delay – 0 overlapping days – 338 days of Applicant delay).

The above-identified application is not subject to a terminal disclaimer. There were no circumstances constituting a failure to engage in reasonable efforts to conclude processing or examination of the application as set forth in 37 C.F.R. § 1.704, other than the circumstances of record.

In summary, Applicants respectfully request an adjustment of patent term under 37 C.F.R. § 1.703 to indicate a total PTA of 340 days. Pursuant to 37 C.F.R. § 1.705(b) and § 1.18(e), the fee required for filing this application for patent term adjustment is believed to be $200.00.

Applicants also submit herewith a petition for a three month extension of time along with the required fee. With the extension, this paper is due on or before September 11, 2017. No additional fees are believed due.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: September 8, 2017

Respectfully submitted,
COOLEY LLP

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1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (617) 937-2300
Fax: (202) 842-7899

By: /Christina K. Stock/
Christina K. Stock
Reg. No. 45,899

150487565 v1

Electronic Patent Application Fee Transmittal

Application Number:	13421769
Filing Date:	15-Mar-2012
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Filer:	Anne Elizabeth Fleckenstein/Jessica Feltz
Attorney Docket Number:	SYPA-009X01US 321994-2142

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
APPLICATION FOR PATENT TERM ADJUSTMENT	2455	1	200	200
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
			Total in USD ($)	**900**

Electronic Acknowledgement Receipt

EFS ID:	30310857
Application Number:	13421769
International Application Number:	
Confirmation Number:	3135
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009X01US 321994-2142
Receipt Date:	08-SEP-2017
Filing Date:	15-MAR-2012
Time Stamp:	15:41:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$900
RAM confirmation Number	091117INTEFSW00002324501283
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Patent Term Adjustment Petition	SYPA-009-X01US_Request_for_Reconsideration_of_PTA.pdf	94911 669a95c778ce865620189f697c6605665809de0e	no	4
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32653 bd8247a22e1aa9b68f26be324f030a7fc43232fe	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	127564		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142	3135

58249 7590 09/22/2017

COOLEY LLP
ATTN: Patent Group
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Suite 700
Washington, DC 20004

EXAMINER
LEE, JIA-HAI

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
09/22/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zpatdcdocketing@cooley.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Patent No. 9,616,097	:	
Comiskey et al.	:	DECISION ON
Issue Date: April 11, 2017	:	PATENT TERM ADJUSTMENT
Application No. 13/421,769	:	
Filed: March 15, 2012	:	
Attorney Docket No.	:	
SYPA-009X01US 321994-2142	:	

This is a decision on patentee's "REQUEST FOR RECONSIDERATION OF PATENT TERM INDICATED ON FACE OF PATENT UNDER 37 C.F.R. §1.705(b)" filed September 8, 2017, requesting that the Office adjust the patent term adjustment from 291 days to 340 days.

This redetermination of patent term adjustment is **GRANTED**.

The Office has re-determined the patent term adjustment to be 340 days.

Relevant Procedural History

On April 11, 2017, this patent issued with a patent term adjustment determination of 291 days. On September 8, 2017, patentee filed this "REQUEST FOR RECONSIDERATION OF PATENT TERM INDICATED ON FACE OF PATENT UNDER 37 C.F.R. §1.705(b)" seeking an adjustment of the determination to 340 days. This request was made timely by an accompanying petition for extension of time within the third month.

Decision

Patentee does not dispute the Office's calculation of "A" delay, "B" delay, "C" delay or overlap. At issue is the period of applicant delay.

Patentee disputes the period of reduction of 71 days, pursuant to 37 CFR 1.704(c)(8), associated with a supplemental response filed September 14, 2016 on the basis that the response was expressly requested by the examiner.

Patentee discloses that instead a period of reduction of 22 days should have been entered, pursuant to 37 CFR 1.704(c)(8),for the filing on July 27, 2016 of an information disclosure statement after the filing of a reply on July 5, 2016.

ON APPLICANT DELAY

The Office has reviewed the disputed calculations of applicant delay and has determined that patentee is correct.

37 CFR 1.704(c)(8) provides for the following reduction for applicant delay:

> Submission of a supplemental reply or other paper, other than a supplemental reply or other paper expressly requested by the examiner, after a reply has been filed, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date the initial reply was filed and ending on the date that the supplemental reply or other such paper was filed;

In this instance, an amendment was filed on July 5, 2016. Thereafter, on July 27, 2016, an information disclosure statement was filed. No 1.704(d) statement was filed. Then, on September 14, 2016, a supplemental amendment was filed. Pursuant to 37 CFR 1.704(c)(8) and given the overlap in the periods of reduction, the Office entered a period of reduction of 71 days.

A review of the record supports a conclusion that the supplemental amendment filed September 14, 2016 was expressly requested by the examiner. Accordingly, no reduction is warranted for the filing of the response on September 14, 2016.

However, a period of reduction of 22 days is warranted for the filing of the IDS on July 27, 2016 as it was filed after the response filed July 5, 2016. The IDS was not expressly requested, and was filed after a reply had been filed on July 5, 2016.

The period of reduction of 71 days is removed. A period of reduction of 22 days is entered.

In view thereof, total applicant delay is 273 [89 + 90 + 94] days.

Overall PTA Calculation

Formula:

"A" delay + "B" delay + "C" delay - Overlap - applicant delay = X

USPTO's Calculation:

383 + 295 + 0 - 0 - 338 = 340

Patentee's Calculation

383 + 295 + 0 - 0 - 338 = 340

Conclusion

Patentee is entitled to PTA of three hundred forty (340) days. Using the formula "A" delay + "B" delay + "C" delay - overlap - applicant delay = X, the amount of PTA is calculated as follows: 383 + 295 + 0 - 0 - 338 = 340 days.

The Office will *sua sponte* issue a certificate of correction. Pursuant to 37 CFR 1.322, the Office will not issue a certificate of correction without first providing assignee or patentee an opportunity to be heard. Accordingly, patentees are given **one (1) month or thirty (30) days**, whichever is longer, from the mail date of this decision to respond. No extensions of time will be granted under § 1.136.

After the expiration of the period of **one (1) month or thirty (30) days**, the Office will sua sponte issue a certificate of correction adjusting the PTA to **three hundred forty (340)** days.

Telephone inquiries specific to this matter should be directed to the undersigned at (571) 272-3219.

/Nancy Johnson/

Nancy Johnson
Attorney Advisor
Office of Petitions

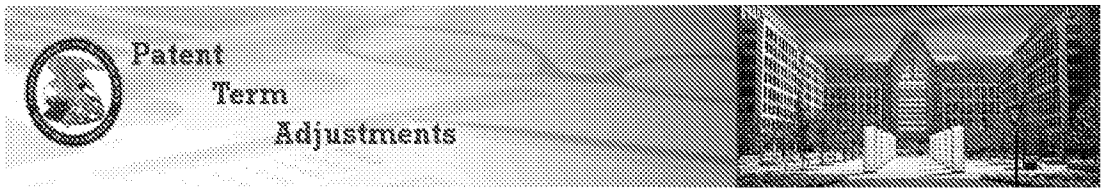
Enclosures: Adjusted PTA calculation
Certificate of Correction

Office of Petitions: Routing Sheet

Application No. 13421769

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**



PTA/PTE Information | Patent Term Adjustment | Patent Term Extension | Calculation Explanation

Application Number*: 13421769 Open Explanation of PTA Calculation Explanation of PTE Calculation

Print

PTA Calculations for Application: 13421769

Application Filing Date:	03/15/2012	OverLapping Days Between (A and B) or (A and C):	0
Issue Date of Patent:	04/11/2017	Non-Overlapping USPTO Delays:	678
A Delays:	383	PTO Manual Adjustment:	49
B Delays:	295	Applicant Delay (APPL):	387
C Delays:	0	Total PTA (days):	340

* - Sorted Column

File Contents History

Action Number	Action Recorded Date	Action Due Date	Action Code	Action Description	Duration PTO	Duration APPL	Patent Action Number
145	09/19/2017		P028	Adjustment of PTA Calculation by PTO		22	0
144	09/19/2017		P028	Adjustment of PTA Calculation by PTO	71		0
138.5	04/11/2017	03/15/2015	PTA36M	PTA 36 Months	295		0.5
138	04/11/2017		PTAC	Patent Issue Date Used in PTA Calculation			0
137	03/08/2017		EFDC	Export to Final Data Capture			0
136	03/07/2017		FIDC	Finished Initial Data Capture			0
135	03/07/2017		PILS	Application Is Considered Ready for Issue			0
134	03/01/2017		N084	Issue Fee Payment Verified			0
133	03/01/2017		CRFT	Sequence Forwarded to Pubs on Tape			0
132	03/01/2017		IFEE	Issue Fee Payment Received			0
131	02/24/2017		EIDC	Export to Initial Data Capture			0
130	02/24/2017		ELC_RVW	Electronic Review			0
129	02/24/2017		EML_NTF	Email Notification			0
128	02/24/2017		MN/=.	Mail Notice of Allowance			0
127	02/21/2017		OAR	Office Action Review			0
126	02/21/2017		OAR	Office Action Review			0
125	02/21/2017		OAR	Office Action Review			0
124	02/21/2017		OAR	Office Action Review			0
123	02/21/2017		IREV	Issue Revision Completed			0
122	02/21/2017		N/=.	Notice of Allowance Data Verification Completed			0
121	02/21/2017		DOCK	Case Docketed to Examiner in GAU			0
120	02/21/2017		DVER	Document Verification			0
118	02/21/2017		EX.R	Reasons for Allowance			0
117	02/21/2017		EX.A	Examiner's Amendment Communication			0
116	02/21/2017		CNTA	Allowability Notice			0
119	02/15/2017		EXET	Interview Summary - Examiner Initiated - Telephonic			0
112	02/01/2017		FWDX	Date Forwarded to Examiner			0
111	01/05/2017		A.NE	Response after Final Action			0
110	10/05/2016		ELC_RVW	Electronic Review			0
109	10/05/2016		EML_NTF	Email Notification			0
108	10/05/2016		MCTFR	Mail Final Rejection (PTOL - 326)			0
107	09/30/2016		OAR	Office Action Review			0
106	09/30/2016		CTFR	Final Rejection			0
104	09/22/2016		EML_NTR	Email Notification			0
102	09/22/2016		PA..	Change in Power of Attorney (May Include Associate POA)			0
101	09/20/2016		FWDX	Date Forwarded to Examiner			0
98	09/16/2016		IDSC	Information Disclosure Statement considered			0
97	09/16/2016		IDSC	Information Disclosure Statement considered			0
96	09/16/2016		IDSC	Information Disclosure Statement considered			0

Action Number	Action Recorded Date	Action Due Date	Action Code	Action Description	Duration PTO	Duration APPL	Parent Action Number
100	09/14/2016	07/05/2016	SA..	Supplemental Response		93	85
105	07/27/2016		M844	Information Disclosure Statement (IDS) Filed			0
88	07/27/2016		WIDS	Information Disclosure Statement (IDS) Filed			0
86	07/07/2016		FWDX	Date Forwarded to Examiner			0
87	07/05/2016		M844	Information Disclosure Statement (IDS) Filed			0
85	07/05/2016	04/04/2016	A...	Response after Non-Final Action		93	76
84	07/05/2016		XT/G	Request for Extension of Time - Granted			0
83	07/05/2016		WIDS	Information Disclosure Statement (IDS) Filed			0
79	01/04/2016		ELC_RVW	Electronic Review			0
78	01/04/2016		EML_NTF	Email Notification			0
76	01/04/2016		MCTNF	Mail Non-Final Rejection			0
82	12/30/2015	11/20/2015	M844	Information Disclosure Statement (IDS) Filed		40	69
81	12/30/2015		RCAP	Reference capture on IDS			0
80	12/30/2015		M844	Information Disclosure Statement (IDS) Filed			0
77	12/30/2015		WIDS	Information Disclosure Statement (IDS) Filed			0
75	12/30/2015		OAR	Office Action Review			0
74	12/29/2015		NAFA125	Add FAOM 1.25 Count			0
73	12/29/2015		NSFA100	Subtract FAOM 1.00 Count			0
72	12/29/2015		CTNF	Non-Final Rejection			0
71	11/24/2015		FWDX	Date Forwarded to Examiner			0
68	11/24/2015		ABN9	Disposal for a RCE / CPA / R129			0
70	11/20/2015		AMSB	Amendment Submitted/Entered with Filing of CPA/RCE			0
69	11/20/2015	08/20/2015	RCEX	Request for Continued Examination (RCE)		93	63
67	11/20/2015		XT/G	Request for Extension of Time - Granted			0
66	11/20/2015		BRCE	Workflow - Request for RCE - Begin			0
65	05/20/2015		ELC_RVW	Electronic Review			0
64	05/20/2015		EML_NTF	Email Notification			0
63	05/20/2015		MCTFR	Mail Final Rejection (PTOL - 326)			0
62	05/18/2015		OAR	Office Action Review			0
61	05/17/2015		CTFR	Final Rejection			0
60	04/27/2015		IDSC	Information Disclosure Statement considered			0
59	02/22/2015		FWDX	Date Forwarded to Examiner			0
58	02/19/2015	11/19/2014	A...	Response after Non-Final Action		93	47
57	02/19/2015		XT/G	Request for Extension of Time - Granted			0
56	02/19/2015		RCAP	Reference capture on IDS			0
55	02/19/2015		M844	Information Disclosure Statement (IDS) Filed			0
54	02/19/2015		AF/D	Affidavit(s) (Rule 131 or 132) or Exhibit(s) Received			0
53	02/19/2015		WIDS	Information Disclosure Statement (IDS) Filed			0
52	10/29/2014		EML_NTR	Email Notification			0
51	10/29/2014		PA..	Change in Power of Attorney (May Include Associate POA)			0
50	10/28/2014		C.AD	Correspondence Address Change			0
49	08/19/2014		ELC_RVW	Electronic Review			0
48	08/19/2014		EML_NTF	Email Notification			0
47	08/19/2014		MCTNF	Mail Non-Final Rejection			0
46	08/14/2014		OAR	Office Action Review			0
45	08/13/2014		CTNF	Non-Final Rejection			0
38	08/07/2014		FWDX	Date Forwarded to Examiner			0
37	08/04/2014		ELC.	Response to Election / Restriction Filed			0
36	06/02/2014		ELC_RVW	Electronic Review			0
35	06/02/2014		EML_NTF	Email Notification			0
34	06/02/2014	05/15/2013	MCTRS	Mail Restriction Requirement	883		0.5
33	05/28/2014		OAR	Office Action Review			0
32	05/27/2014		CTRS	Restriction/Election Requirement			0
29	04/23/2014		DOCK	Case Docketed to Examiner in GAU			0
28	04/23/2014		DOCK	Case Docketed to Examiner in GAU			0
26	10/07/2013		DOCK	Case Docketed to Examiner in GAU			0
22	09/21/2012		EML_NTR	Email Notification			0
21	09/20/2012		PG-ISSUE	PG-Pub Issue Notification			0
20	08/31/2012		DOCK	Case Docketed to Examiner in GAU			0
19	08/30/2012		DOCK	Case Docketed to Examiner in GAU			0
18	08/03/2012		DOCK	Case Docketed to Examiner in GAU			0
16	07/11/2012		OIPE	Application Dispatched from OIPE			0
15	06/14/2012		COMP	Application Is Now Complete			0
14	06/14/2012		CRFE	CRF Is Good Technically / Entered into Database			0
13	06/14/2012		PA..	Change in Power of Attorney (May Include Associate POA)			0
12	06/14/2012		PGPC	Sent to Classification Contractor			0
11	06/14/2012		FLRCPT.U	Filing Receipt - Updated			0
17	06/04/2012		A.PE	Preliminary Amendment			0
10	06/04/2012		FLFEE	Payment of additional filing fee/Preexam			0
9	06/04/2012		SEQLIST	A set of symbols and procedures, provided to the PTO on a set of computer listings, that describe in			0

Action Number	Action Recorded Date	Action Due Date	Action Code	Action Description	Duration PTO	Duration APPL	Parent Action Number
8	06/04/2012		CRFL	CRF Disk Has Been Received by Preexam / Group / PCT			0
7	06/04/2012		SES	Small Entity Statement (37 CFR 1.27)			0
6	06/04/2012		OATHDECL	A statement by one or more inventors satisfying the requirement under 35 USC 115, Oath of the Applic			0
5	04/03/2012		INCD	Notice Mailed--Application Incomplete--Filing Date Assigned			0
4	04/03/2012		FLRCPT.O	Filing Receipt			0
3	03/17/2012		L194	Cleared by OIPE CSR			0
2	03/15/2012		SCAN	IFW Scan & PACR Auto Security Review			0
1	03/15/2012		IEXX	Initial Exam Team nn			0
0.5	03/15/2012		EFILE	Filing date			0

Export to: Excel

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT : 9,616,097

DATED : **April 11, 2017**

INVENTOR(S) : Comiskey et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 USC 154(b) by 291 days

Delete the phrase "by 291 days" and insert – by 340 days--

Office of Petitions: Decision Count Sheet

Mailing Month: 9

Application No.: 13421769

13421769

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456

For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: Nancy Johnson

Count (1) - Palm Credit 13421769

Decision: GRANT

FINANCE WORK NEEDED
☐ Select Check Box for YES

GRANT

Decision Type: 551 - 37 CFR 1.705(d) - PATENT TERM ADJUSTMENT A

551

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: 9/19/2017

Office of Petitions Internal Document - Ver. 5.0

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,616,097 B2
APPLICATION NO. : 13/421769
DATED : April 11, 2017
INVENTOR(S) : Comiskey et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 340 days.

Signed and Sealed this
Twenty-fifth Day of September, 2018

Andrei Iancu
Director of the United States Patent and Trademark Office

PTO/SB/81A (12-08)
Approved for use through 03/31/2012. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	9,616,097
Issue Date	April 11, 217
First Named Inventor	Stephen Comiskey
Title	Formulations of Guanylate Cyclase C Agonists and Methods of Use
Attorney Docket No.	376464-2005US1 (00107)

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

162421

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-identified Customer Number.

OR

☐ The address associated with the Customer Number identified in the box at right.

OR

☐ Firm or Individual Name	
Address	
City	State / Zip
Country	
Telephone	Email

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature		Date	August 22, 2019
Name	Robert Gonder	Telephone	
Title and Company	VP and Associate General Counsel, IP, Bausch Health Ireland Limited		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☐ A total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/96 (11-18)
Approved for use through 11/30/2020. OMB 0651-0031
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Synergy Pharmaceuticals, Inc.

Application No./Patent No.: 9,616,097 Filed/Issue Date: April 11, 2017

Titled:
Formulations of Guanylate Cyclase C Agonists and Methods of Use

BAUSCH HEALTH IRELAND LIMITED, a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel_____, Frame_____, or a copy* is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: inventors To: Synergy Pharmaceuticals, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 028079, Frame 0873, or a copy* is attached.

2. From: Synergy Pharmaceuticals, Inc. To: Bausch Health Ireland Limited
The document was recorded in the United States Patent and Trademark Office at
Reel_____, Frame_____, or a copy* is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel_____, Frame_____, or a copy* is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ *As required by 37 CFR 3.73(b)(1)(i), if a copy/copies is/are attached, the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Domingos J. Silva/ September 28, 2020
Signature Date

Domingos J. Silva 64197
Printed or Typed Name Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT ASSIGNMENT AGREEMENT – UNITED STATES

THIS PATENT PROPERTY ASSIGNMENT AGREEMENT – UNITED STATES, dated as of March 6, 2019 (this "Agreement"), is made by and among Bausch Health Ireland Limited, a private limited company organized under the laws of Ireland (the "Assignee"), and Synergy Pharmaceuticals Inc., a Delaware corporation (the "Parent"), and its wholly-owned subsidiary, Synergy Advanced Pharmaceuticals, Inc., a Delaware corporation ("SF Sub") (each of the Parent and SF Sub, an "Assignor" and collectively, the "Assignors"). Each of the Assignee and the Assignors are referred to individually herein as a "Party" and collectively as the "Parties." Capitalized terms used herein and not otherwise defined shall have the respective meanings set forth in the Asset Purchase Agreement (as defined below).

RECITALS:

WHEREAS, the Assignee and the Assignors have entered into that certain Asset Purchase Agreement, dated as of December 11, 2018, as amended and restated on January 4, 2019 (as further amended, restated, supplemented or otherwise modified from time to time, the "Asset Purchase Agreement"); and

WHEREAS, this Agreement is made and delivered pursuant to the terms and subject to the conditions set forth in the Asset Purchase Agreement.

AGREEMENT:

NOW, THEREFORE, subject to the terms and conditions of the Asset Purchase Agreement, and in consideration of the representations, warranties, covenants and agreements set forth therein, the Parties hereto agree as follows:

1. Acquired Patents. For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Assignors hereby irrevocably and unconditionally sell, transfer, assign, convey, and deliver to the Assignee and its successors and permitted assigns, forever, and the Assignee accepts and acquires from the Assignors all of the Assignors' right, title, and interest (of every nature, kind, and description, tangible or intangible (including goodwill), whether real, personal, or mixed, whether accrued, contingent, or otherwise, wherever located), in each case free and clear of any and all Encumbrances (other than Permitted Post-Closing Encumbrances) in, to, and under all of Seller's right, title and interest in and to those patents and patent applications set forth on Schedule I hereto (the "Acquired Patents"), including (i) all of Assignors' rights in and to all income, royalties, damages and payments now or hereafter due or payable with respect thereto, (ii) all causes of action (whether in law or in equity) with respect thereto, and (iii) the right to sue, counterclaim, and recover for past, present and future infringement of the Acquired Patents.

2. Further Assurances. This Agreement has been executed and delivered by the Assignors with the agreement that the same may be recorded with the United States Patent and Trademark Office and with other applicable governmental entity or registrar in other jurisdictions outside the United States. From time to time hereafter, and without further consideration, each of the Assignors, the Assignee, and their respective successors and permitted

assigns, covenant and agree that each of the Assignors, the Assignee, and their respective successors and permitted assigns shall execute and deliver, or shall cause to be executed and delivered, such further instruments of conveyance and transfer and take such additional action as the other Party may reasonably request to effect, consummate, confirm, or evidence the transfer to the Assignee, its successors, and permitted assigns of the Acquired Patents in accordance with the foregoing. Assignor shall provide Assignee and its successors and assigns reasonable cooperation and assistance at Assignee's request and expense (including the execution and delivery of any and all country specific forms of assignment, affidavits, declarations, oaths, exhibits, powers of attorney or other documentation) as are reasonably requested by Assignee to effect, record, register or maintain this Assignment and/or the rights assigned herein. The Parties hereby authorize the relevant authority at the United States Patent and Trademark Office and respective foreign patent and trademark offices to record this Agreement and record Assignee as the owner of the Acquired Patents and to issue any and all Acquired Patents to Assignee, as assignee of Assignor's entire right, title and interest in, to and under the same.

3. Power of Attorney. The Assignors hereby constitute and appoint the Assignee as the Assignors' true and lawful attorney in fact, with full power of substitution in the Assignors' name and stead, to take any and all steps, including proceedings at law, in equity or otherwise, to execute, acknowledge and deliver any and all instruments and assurances necessary or expedient in order to vest or perfect the aforesaid rights more effectively in the Assignee or to protect the same or to enforce any claim or right of any kind with respect thereto. The Assignors hereby declare that the foregoing power is coupled with an interest and as such is irrevocable.

4. Notices. All notices, requests, claims, demands or other communications hereunder to any Party shall be given in the manner set forth in the Asset Purchase Agreement. Any Party may change its address for receiving notices, requests, and other documents by giving written notice of such change to the other Parties in accordance with the Asset Purchase Agreement.

5. Severability. If any provision of this Agreement or the application thereof to any Person or circumstance is held invalid or unenforceable, the remainder of this Agreement, and the application of such provision to other Persons or circumstances, shall not be affected thereby, and to such end, the provisions of this Agreement are agreed to be severable.

6. Effectiveness. This Agreement shall be effective as of the Closing Date pursuant to the terms of the Asset Purchase Agreement.

7. Amendments; Waivers. This Agreement may not be waived, altered, amended or modified except by an instrument in writing signed by, or on behalf of each of the Parties hereto.

8. Counterparts. This Agreement may be executed in two or more counterparts, each of which shall be deemed to be an original but all of which shall constitute one and the same agreement.

9. Governing Law; Submission of Jurisdiction; Waiver of Jury Trial. With regard to patent, trademark and copyright issues, this Agreement shall be governed by and construed in accordance with the federal Laws of the United States. For all other matters, this Agreement shall be governed by and construed in accordance with the Laws of the State of Delaware

without regard to the rules of conflict of Laws of the State of Delaware or any other jurisdiction. Each of the Parties irrevocably and unconditionally consents to submit to the exclusive jurisdiction of the Bankruptcy Court for any litigation arising out of or relating to this Agreement and the transactions contemplated thereby (and agrees not to commence any litigation relating thereto except in the Bankruptcy Court), provided, however, that if the Chapter 11 Case has been closed and/or the Bankruptcy Court declines jurisdiction, each of the Parties agree to and hereby irrevocably and unconditionally consents to submit to the exclusive jurisdiction of the United States District Court sitting in Wilmington, Delaware. Each of the Parties irrevocably and unconditionally waives any objection to the laying of venue of any such litigation in any such court. Each Party hereby consents to service of process in the manner set forth in Section 4. EACH PARTY HERETO IRREVOCABLY AND UNCONDITIONALLY WAIVES ANY RIGHT IT MAY HAVE TO A TRIAL BY JURY IN RESPECT OF ANY LITIGATION ARISING OUT OF OR RELATING TO THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED HEREBY.

10. Third Parties. This Agreement will be binding upon, inure to the benefit of and be enforceable by the Parties hereto and their respective successors and permitted assigns and shall not be binding upon, inure to the benefit of, or be enforceable by any other party.

[*Signature Pages Follow*]

IN WITNESS WHEREOF, the Parties have caused this Assignment to be executed by their respective officers thereunto duly authorized as of the date first above written.

ASSIGNORS:

SYNERGY PHARMACEUTICALS INC.

By: _____
Name: Gary G. Gemignani
Title: EVP and Chief Financial Officer

SYNERGY ADVANCED PHARMACEUTICALS, INC.

By: _____
Name: Gary G. Gemignani
Title: EVP and Chief Financial Officer

STATE OF Connecticut)
: ss.: Darien
COUNTY OF Fairfield)

On this 4th day of March 2019, before me personally appeared Gary G Gemignani, in his/her capacity as EVP and CFO of Synergy Pharmaceuticals Inc., and Gary G Gemignani, in his/her capacity as EVP and CFO of Synergy Advanced Pharmaceuticals, Inc.., who each proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is subscribed to or who executed the foregoing instrument in his authorized capacity, and who duly acknowledged to me that execution of the same is his/her own free act and deed and made with appropriate authority.

_____
Notary Public

MICHAEL HENRY BERGMANN
Notary Public
Connecticut
My Commission Expires Mar 31, 2019

My Commission Expires: 03/31/2019

[Notary Seal]

[Signature Page to Patent Assignment – United States]

IN WITNESS WHEREOF, the Parties have caused this Assigment to be executed by their respective officers thereunto duly authorized as of the date first above written.

ASSIGNEE:

BAUSCH HEALTH IRELAND LIMITED

By: _____
Name: Graham Jackson
Title: Director

[Signature Page to Patent Assignment – United States]

Schedule I

Acquired Patents

Title/Mark	Application No.	Application Date	Registration No.	Registration Date	Case Status	Country
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	10/107,814	3/28/2002	7,041,786	5/9/2006	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	11/347,115	2/2/2006	7,799,897	9/21/2010	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	12/763,707	4/20/2010	8,114,831	2/14/2012	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	13/339,785	12/29/2011	8,637,451	1/28/2014	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	14/137,256	12/20/2013			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/133,344	6/4/2008	7,879,802	2/1/2011	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA, ATHEROSCLEROSIS, CORONARY HEART DISEASE, GALLSTONE, OBESITY AND OTHER CARDIOVASCULAR DISEASES	12/630,654	12/3/2009	8,969,514	3/3/2015	Granted	United States of America

AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/010,267	1/20/2011	8,716,224	5/6/2014	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/857,283	4/5/2013	8,901,075	12/2/2014	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/528,257	10/30/2014	9,266,926	2/23/2016	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA, ATHEROSCLEROSIS, CORONARY HEART DISEASE, GALLSTONE, OBESITY AND OTHER CARDIOVASCULAR DISEASES	14/742,456	6/17/2015	9,814,752	11/14/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/049,740	2/22/2016	9,914,752	3/13/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/471,462	3/28/2017			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/918,047	3/12/2018			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/228,843	3/28/2014	9,238,677	1/19/2016	Granted	United States of America

METHOD OF INHIBITING BILE ACID ABSORPTION BY ADMINISTERING AN AGONIST OF A GUANYLATE CYCLASE RECEPTOR	13/513,224	12/3/2010	9,089,612	7/28/2015	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/478,505	6/4/2009	8,207,295	6/26/2012	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/467,703	5/9/2012	8,357,775	1/22/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/716,874	12/17/2012	8,497,348	7/30/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/831,293	8/20/2015	9,920,095	3/20/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/504,288	7/16/2009	8,034,782	10/11/2011	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/632,314	2/26/2015	9,505,805	11/29/2016	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/226,300	9/6/2011	8,367,800	2/5/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/731,483	12/31/2012	8,569,246	10/29/2013	Granted	United States of America

AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/955,710	7/31/2013	8,664,354	3/4/2014	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	14/301,812	6/11/2014	10,034,836	7/31/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	16/018,278	6/26/2018			Pending	United States of America
PROCESS OF PREPARING GUANYLATE CYCLASE C AGONIST	15/405,787	1/13/2017			Pending	United States of America
PROCESS OF PREPARING GUANYLATE CYCLASE C AGONIST	14/001,638	3/1/2012	9,580,471	2/28/2017	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	14/845,644	9/4/2015	9,610,321	4/4/2017	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/467,631	3/23/2017	9,925,231	3/27/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/467,648	3/23/2017	9,919,024	3/20/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/924,940	3/19/2018			Pending	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	13/421,769	3/15/2012	9,616,097	4/11/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR DOWNREGULATION OF PRO-INFLAMMATORY CYTOKINES	15/026,560	10/9/2014			Pending	United States of America
COMPOSITIONS USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS	14/207,749	3/13/2014	9,486,494	11/6/2016	Granted	United States of America

COMPOSITIONS USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS	15/272,873	9/22/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	14/189,645	2/25/2014	9,545,446	1/17/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	15/381,680	12/16/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	14/207,753	3/13/2014	9,708,367	7/18/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	15/622,526	6/14/2017	10,118,946	11/6/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	16/150,703	10/3/2018			Pending	United States of America
FORMULATIONS AND METHODS FOR TREATING ULCERATIVE COLITIS	16/069,313	1/11/2017			Pending	United States of America
COMPOSITIONS AND METHOD FOR THE TREATMENT AND DETECTION OF COLON CANCER	15/777,273	11/18/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF OPIOID INDUCED DYSFUNCTIONS	15/026,563	10/10/2014			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF OPIOID INDUCED DYSFUNCTIONS	14/944,499	11/18/2015			Pending	United States of America
ULTRA-PURE AGONISTS OF GUANYLATE CYCLASE C, METHOD OF MAKING AND USING SAME	16/000,251	6/5/2018			Pending	United States of America
ULTRA-PURE AGONISTS OF GUANYLATE CYCLASE C, METHOD OF MAKING AND USING SAME	14/896,019	6/5/2014	10,011,637	7/3/2018	Granted	United States of America

INTER PARTES REVIEW OF USP 8,101,579 ENTITLED METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS (IPR 2018-01363)			8,101,579		Pending	United States of America

Electronic Acknowledgement Receipt

EFS ID:	40687011
Application Number:	13421769
International Application Number:	
Confirmation Number:	3135
Title of Invention:	Formulations of Guanylate Cyclase C Agonists and Methods of Use
First Named Inventor/Applicant Name:	Stephen Comiskey
Customer Number:	58249
Filer:	Domingos J. Silva/Catherine Rose
Filer Authorized By:	Domingos J. Silva
Attorney Docket Number:	SYPA-009X01US 321994-2142
Receipt Date:	28-SEP-2020
Filing Date:	15-MAR-2012
Time Stamp:	14:01:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	General_Patent_POA_373b.pdf	225565 176a8347c42edf304d9affb55377c956270b1fd4	no	2

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	Statement_373b_Assignment.pdf	346349 8d595156ad5d576ed9e93dbd8e16f4fd35d60d57	no	13
Warnings:					
Information:					
			Total Files Size (in bytes):	571914	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
13/421,769	03/15/2012	Stephen Comiskey	376464-2005US1 (00107)	122229

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 09/30/2020 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Domingos J. Silva/
Name:	DOMINGOS J. SILVA
Registration Number:	64197

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/421,769	03/15/2012	Stephen Comiskey	SYPA-009X01US 321994-2142

CONFIRMATION NO. 3135

POWER OF ATTORNEY NOTICE

58249
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Date Mailed: 10/02/2020

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/28/2020.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/agizaw/

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Alexandria, Virginia 22313-1450
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13/421,769	03/15/2012	Stephen Comiskey	376464-2005US1 (00107)

CONFIRMATION NO. 3135

POA ACCEPTANCE LETTER

162421
SAUL EWING ARNSTEIN & LEHR LLP (Bausch Health)
Attn: Patent Docket Clerk, Centre Square West,
1500 Market Street, 38th Floor
Philadelphia, PA 19102-2186

OC000000120312261

Date Mailed: 10/02/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/28/2020.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/agizaw/

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,041,786	5/9/2006	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	7,799,897	9/21/2010	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	8,637,451	1/28/2014	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4	9,610,321	4/4/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
5	9,616,097	4/11/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

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3	10,011,637	7/3/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above---entitled case, the following patent(s)/ trademark(s) have been included:

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PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above---entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Notice of Voluntary Dismissal

CLERK	(BY) DEPUTY CLERK	DATE
John A Cerino		5-6-2021

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Page 2 of 2

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

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2	9,925,231	3/27/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	10,011,637	7/3/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**