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(54) Title: LINACLOTIDE FOR THE TREATMENT OF CHRONIC CONSTIPATION

(57) Abrégé/Abstract:
The invention provides methods for treating a patient with chronic constipation by administering a therapeutically effective dose of linaclotide.

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(54) Title: LINACLOTIDE FOR THE TREATMENT OF CHRONIC CONSTIPATION

(57) Abstract: The invention provides methods for treating a patient with chronic constipation by administering a therapeutically effective dose of linaclotide.

LINACLOTIDE FOR THE TREATMENT OF CHRONIC CONSTIPATION

FIELD OF THE INVENTION

[0001] This invention relates to the use of linaclotide to treat chronic constipation.

PRIORITY CLAIM

[0002] This application claims priority to U.S. Provisional Patent Application Serial No. 61/257,463, filed November 03, 2009; U.S. Provisional Patent Application Serial No. 61/257,465, filed November 03, 2009; U.S. Provisional Patent Application Serial No. 61/327,094, filed April 22, 2010; U.S. Provisional Patent Application Serial No. 61/330,124, filed April 30, 2010, and U.S. Provisional Patent Application Serial No. 61/394,181, filed October 18, 2010. The entire contents of the aforementioned applications are incorporated herein by reference.

BACKGROUND

[0003] As many as 34 million Americans suffer from symptoms associated with chronic constipation (CC) and 8.5 million patients have sought treatment. Patients with CC often experience hard and lumpy stools, straining during defecation, a sensation of incomplete evacuation, and fewer than three bowel movements per week. The discomfort and bloating of CC significantly affects patients' quality of life by impairing their ability to work and participate in typical daily activities.

[0004] Chronic constipation in a patient may be defined as the presence of fewer than three bowel movements (BMs) per week and by one or more of the following symptoms for at least 12 weeks, which need not be consecutive, in the 12 months before starting chronic treatment with tegaserod, lubiprostone, polyethylene glycol 3350 or any laxative:

a) Straining during greater than 25% of BMs;

b) Lumpy or hard stool during greater than 25% of BMs; and

c) Sensation of incomplete evacuation during greater than 25% of BMs (see, e.g., Rome II criteria (Drossman, 2000), slightly modified from the original).

[0005] Half of CC patients are not satisfied with currently available treatments for CC. Thus, there remains a need for new compounds and methods of treating CC.

SUMMARY

[0006] In general, the invention relates to a method of treating chronic constipation.

[0007] In one aspect, the method of treating a patient with chronic constipation includes administering a therapeutically effective dose of linaclotide once a day.

[0008] In another aspect, the invention relates to a method of optimizing a treatment of chronic constipation in a patient with linaclotide.

[0009] In one aspect, the method includes:

a) administering a first therapeutically effective dose of linaclotide once a day;

b) determining whether the patient develops loose stools or diarrhea after treatment with linaclotide;

c) wherein if the patient develops loose stools or diarrhea after one or more days of said administering, administering a second therapeutically effective dose of linaclotide once a day, wherein said second therapeutically effective dose is lower than said first therapeutically effective dose.

[00010] In still another aspect, a method of optimizing the treatment with linaclotide of a patient with chronic constipation, includes:

a) administering a first therapeutically effective dose of linaclotide once a day on a first schedule;

b) determining whether the patient develops loose stools or diarrhea after treatment with linaclotide;

c) wherein if the patient develops loose stools or diarrhea after one or more days of said administering, administering a second therapeutically effective dose of linaclotide on a second schedule that is less frequent than the first schedule.

[00011] In yet another aspect, a method of optimizing the treatment of a patient with chronic constipation, includes:

a) administering a first dose of linaclotide once a day on a first schedule to the patient; and

b) determining whether the administering increases the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week;

c) wherein if the patient has fewer than three CSBMs per week, administering a second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

[00012] In a further aspect, a method of optimizing the treatment of a patient with chronic constipation, includes:

(a) administering an amount of linaclotide once a day on a daily basis to the patient; and

(b) determining whether the patient develops loose stools or diarrhea;

wherein the presence of loose stools or diarrhea indicates a need to decrease the amount of linaclotide subsequently administered to said patient and/or decrease the dosing frequency when linaclotide is subsequently administered to said patient.

[00013] In another aspect, a method of optimizing the treatment of a patient with chronic constipation, includes:

(a) administering a first amount of linaclotide once a day at a first frequency to the patient; and

(b) determining whether the administering increases the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week;

wherein the patient having fewer than three CSBMs per week indicates a need to increase second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

[00014] In certain embodiments of the foregoing aspects, the methods include administering linaclotide formulation including:

(a) linaclotide or pharmaceutically acceptable salts thereof;

(b) $CaCl_2$;

(c) L-Leucine; and

(d) Hydroxypropyl Methylcellulose

wherein linaclotide is present in the pharmaceutical composition in an amount between 100 µg to 600 µg and the molar ratio of Ca^{2+}:leucine:linaclotide is between 5-100:5-50:1.

[00015] In some aspects of the present methods, administering of linaclotide provides sustained relief from symptoms of chronic constipation, sustained relief from symptoms of chronic constipation for at least 16 weeks, sustained relief from symptoms of chronic constipation for at least 1 out of 2 weeks, sustained relief of symptoms of chronic constipation for at least 3 out of 4 weeks, 6 out of 12 weeks, or 9 out of 16 weeks.

[00016] Importantly, administration of linaclotide as described herein provides one or more of the following advantages: an increase in the rate, for example frequency, of spontaneous bowel movements (SBMs) and complete spontaneous bowel movements (CSBMs) by the patient compared to said patient prior to treatment with linaclotide; a decrease in bloating, such as abdominal bloating, in said patient compared to said patient prior to treatment with linaclotide; a decrease in the abdominal discomfort in said patient compared to said patient prior to treatment with linaclotide; a decrease in the constipation severity in said patient compared to said patient prior to treatment with linaclotide; an improvement in the stool

consistency in said patient compared to said patient prior to treatment with linaclotide, a decrease in the straining during defecation in said patient compared to said patient prior to treatment with linaclotide; an improvement in patient assessment of quality of life with constipation; and discontinuing linaclotide administration did not produce a rebound or exacerbation of chronic constipation symptoms.

[00017] Further, said patient may exhibit at least one SBM or CSBM within one week, 72 hours, 48 hours, or 24 hours after the administering of a therapeutically effective amount of linaclotide. Administering of a therapeutically effective amount of linaclotide may also produce an improvement in any of SBM rate, CSBM rate, stool consistency, straining, abdominal discomfort, bloating, constipation severity, or a combination thereof, within one week, 72 hours, 48 hours, or 24 hours post-administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[00018] Figure 1 depicts the Trial 2 study design.

[00019] Figure 2 depicts the results and improvements of the weekly CSBM rate from Trial 2 for both the treatment period and randomized withdrawal period.

[00020] Figure 3 depicts the results and improvements of the weekly SBM rate from Trial 2 for both the treatment period and randomized withdrawal period.

[00021] Figure 4 depicts the results and improvements of the weekly SBM rate from Trial 1 and 2 during the treatment periods for placebo, 133 μg linaclotide and 266 μg linaclotide.

[00022] Figure 5 depicts the results and qualitative improvement of stool consistency during the 12 week administration of linaclotide in Trials 1 and 2 as described herein.

[00023] Figure 6 depicts the results and qualitative improvement in the severity of straining during defecation for the 12 week administration of linaclotide in Trials 1 and 2.

[00024] Figure 7 depicts the results and qualitative improvement of bloating during the 12 week administration of linaclotide in Trials 1 and 2.

[00025] Figure 8 depicts the results and qualitative improvement of abdominal discomfort during the 12 week administration of linaclotide in Trials 1 and 2.

[00026] Figure 9 depicts the results and qualitative improvement of constipation severity during the 12 week administration of linaclotide in Trials 1 and 2.

[00027] Figure 10 depicts the results and qualitative improvement in PAC-QOL during the 12 week administration of linaclotide in Trials 1 and 2.

[00028] Figure 11 depicts the results of the CSBM overall responder rate of patients in at least six out of 12 weeks with an increase of ≥1 from baseline in weekly CSBMs for both Trial 1 and 2.

[00029] Figure 12a depicts the percentages of patients in Trials 1 and 2 reporting at least one SBM within 24 hours of initial dose of the initial treatment with placebo, 133 μg, or 266 μg linaclotide; Figure 12b depicts the percentages of patients reporting at least one CSBM within 24 hours of initial dose.

[00030] Figure 13 depicts an example of an analysis of a sample containing linaclotide by HPLC.

[00031] These figures are provided by way of examples and are not intended to limit the scope of the present invention.

DETAILED DESCRIPTION

Definitions

[00032] As used herein, the term "binder" refers to any pharmaceutically acceptable binder that may be used in the practice of the invention. Examples of pharmaceutically acceptable binders include, without limitation, a starch (e.g., corn starch, potato starch and pre-gelatinized starch (e.g., STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd. and other starches), maltodextrin, gelatin, natural and synthetic gums such as acacia, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., methylcellulose, hydroxyethyl cellulose, hydroxyethyl methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose (hypromellose), ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, carboxymethylcellulose, microcrystalline cellulose (e.g., AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA)), polyvinyl alcohol, polyvinyl pyrrolidone (e.g., polyvinyl pyrrolidone K30), and mixtures thereof.

[00033] As used herein, the term "filler" refers to any pharmaceutically acceptable filler that may be used in the practice of the invention. Examples of pharmaceutically acceptable fillers include, without limitation, talc, calcium carbonate (e.g., granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (e.g., granules or powder), microcrystalline cellulose (e.g., Avicel PH101 or Celphere CP-305), powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch (e.g., Starch 1500), pre-gelatinized starch, lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, isomalt, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, xylitol, myoinositol, and mixtures thereof.

[00034] Examples of pharmaceutically acceptable fillers that may be particularly used for coating with linaclotide include, without limitation, talc, microcrystalline cellulose (e.g., Avicel PH101 or Celphere CP-305), powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, isomalt, dibasic calcium phosphate, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, xylitol, mannitol, myoinositol, and mixtures thereof.

[00035] As used herein, the term "additives" refers to any pharmaceutically acceptable additive. Pharmaceutically acceptable additives include, without limitation, disintegrants, dispersing additives, lubricants, glidants, antioxidants, coating additives, diluents, surfactants, flavoring additives, humectants, absorption promoting additives, controlled release additives, anti-caking additives, anti-microbial agents (e.g., preservatives), colorants, desiccants, plasticizers and dyes.

[00036] As used herein, an "excipient" is any pharmaceutically acceptable additive, filler, binder or agent.

[00037] As used herein, "spontaneous bowel movement" of SBM, is a bowel movement that occurs in the absence of laxative, enema, or suppository usage within the preceding 24 hours.

[00038] As used herein, a "complete spontaneous bowel movement" or CSBM is an SBM that is accompanied by the patient self-reporting a feeling of complete emptying of the bowel.

[00039] As used herein, a "CSBM weekly responder" is a patient who had a three or more CSBMs per week and an increase of at least one CSBM per week over baseline.

[00040] As used herein, a "12-week CSBM overall responder" is a patient who is a CSBM weekly responder for at least nine of the 12 weeks of the treatment period.

[00041] As used herein, "Bristol Stool Form Scale" or BSFS is seven-point scale measuring stool consistency. BSFS is a surrogate marker of gastrointestinal transit time.

[00042] As used herein, "PAC-QOL" is the Patient Assessment of Constipation-Quality of Life with 28 questions developed through literature, qualitative interviews, and clinician review. The assessment was grouped into 4 subscales including physical discomfort (4 items); psychosocial discomfort (8 items); worries/concerns (11 items); satisfaction (5 items). Scoring for overall score for PAC-QOL is based on the average of responses to 28 items wherein a lower score represents a higher quality of life (QOL). Subscale scoring is based on the average score of individual items in the subscale wherein a lower score represents a higher quality of life (QOL).

[00043] As used herein, "rebound" is the exacerbation of the severity of a symptom experienced by a patient after discontinuation of a treatment as compared to the severity of the symptom experienced by the patient prior to that treatment.

[00044] As used herein, "rapid relief" is the improvement of one or more symptoms described herein within one week of initiating a treatment as described herein.

Guanylate Cyclase

[00045] Guanylate cyclase C (GC-C) is a transmembrane receptor that is located on the apical surface of epithelial cells in the stomach and intestine. The receptor has an extracellular ligand-binding domain, a single transmembrane region and a C-terminal guanylyl cyclase domain. When a ligand binds to the extracellular domain of GC-C, the intracellular catalytic domain catalyzes the production of cGMP from GTP. *In vivo*, this increase in intracellular cGMP initiates a cascade of events that leads to increased secretion of chloride and bicarbonate into the intestinal lumen, increased luminal pH, decreased luminal sodium absorption, increased fluid secretion, and acceleration of intestinal transit. cGMP, which is secreted bidirectionally from the epithelium into the mucosa and lumen, has also been shown to dampen afferent C fiber firing, suggesting a potential mechanism for the observed analgesic effects of GC-C agonists on visceral pain.

[00046] Linaclotide is a peptide GC-C agonist that is orally administered and currently in clinical trials for treatment of irritable bowel syndrome with constipation (IBS-c) and CC. In Phase 2b studies for CC, linaclotide reduced constipation, abdominal discomfort, and bloating throughout the four-week treatment period. Orally administered linaclotide acts locally by activating GC-C at the luminal surface; there are no detectable levels of linaclotide seen systemically after oral administration at therapeutic dose levels.

[00047] Linaclotide is a 14 amino acid peptide having the sequence 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} with disulfide bonds between Cys_1 and Cys_6, between Cys_2 and Cys_{10} and between Cys_5 and Cys_{13}.

[00048] The dose range of linaclotide for adult humans is generally from 25 µg to 6 mg per day orally. In a further embodiment, the dose range is 25 µg to 2 mg per day orally. In some embodiments, the dose range for adult humans is 50 µg to 1 mg per day orally (e.g., 50 µg, 67.5 µg, 100 µg, 133 µg, 150 µg, 200 µg, 250 µg, 266 µg, 300 µg, 350 µg, 400 µg, 450 µg, 500 µg, 550 µg, 600 µg, 650 µg, 700 µg, 750 µg, 800 µg, 850 µg, 900 µg, 950 µg or 1 mg). In further embodiments, the dose range is 100 µg to 600 µg per day orally. In other embodiments, the dose is 50 µg, 67.5 µg, 100 µg, 133 µg, 150 µg, 200 µg, 266 µg, 300 µg, 400 µg, 500 µg or 600 µg linaclotide per day orally.

Administration of peptides and GC-C receptor agonists

[00049] For treatment of gastrointestinal disorders, the peptides and agonists of the invention are preferably administered orally, e.g., as a tablet, gel, paste, sachet, a pellet, a capsule, a slurry, a liquid, a powder or in some other form. Orally administered compositions can include, for example, binders, lubricants, inert diluents, lubricating, surface active or dispersing additives, flavoring additives, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the linaclotide therein. The linaclotide can be co-administered or co-formulated with other medications. In one embodiment, the linaclotide composition can be co-administered with other medications used to treat gastrointestinal disorders.

[00050] In certain embodiments, the linaclotide composition is provided in a unit dosage form. In some embodiments, the unit dosage form is a capsule, a tablet, a sachet, a pellet or a powder. In one such embodiment, the unit dosage form is a capsule or tablet. Such unit dosage forms may be contained in a container such as, without limitation, a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. It is feasible that more than one container can be used together in a single package to provide a single dosage form. For example, tablets or capsules may be contained in a bottle which is in turn contained within a box. In some embodiments, the unit dosage forms are provided in a container further comprising a desiccant. In a further embodiment, the unit dosage forms, e.g., a quantity of tablets or capsules, are provided in a container, e.g., a bottle, jar or re-sealable bag, containing a desiccant. In a further embodiment, the container containing the unit dosage forms is packaged with administration or dosage instructions. In certain embodiments, the linaclotide composition is provided in a kit. The linaclotide composition described herein and combination therapy agents can be packaged as a kit that includes single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, the linaclotide composition can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions.

[00051] In various embodiments, the unit dosage form is administered with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g., with breakfast). In various embodiments, the unit dosage form is administered once a day, twice a day or three times a day. The unit dosage form can optionally comprise other additives. In

some embodiments, one, two or three unit dosage forms will contain the daily oral dose of linaclotide. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

Methods of Treating Chronic Constipation

[00052] In some aspects, the invention provides a method of treating a patient with chronic constipation, comprising administering a therapeutically effective dose of linaclotide once a day.

[00053] In some embodiments, the therapeutically effective dose is administered once a day in the morning.

[00054] In other embodiments, the therapeutically effective dose is administered at least 30 minutes before ingestion of food.

[00055] In still other embodiments, the therapeutically effective dose is 100 to 600 μg linaclotide. For instance, in some specific embodiments, the therapeutically effective dose is 133 μg or 266 μg of linaclotide.

[00056] In some embodiments, the method includes administering linaclotide for a period of greater than four weeks. In some embodiments, the method includes administering linaclotide for a period of greater than six weeks. For instance, in some specific embodiments, linaclotide is administered for a period of at least 6 weeks.

[00057] In some embodiments, linaclotide is administered for a period of at least 12 weeks.

[00058] In some instances, linaclotide is administered each day of the week. In other instances, linaclotide is administered at least once a week, at least twice a week, at least three times a week, at least four times a week, at least five times a week or at least six times a week.

[00059] In some aspects, the method of treating chronic constipation includes administering a formulation containing:

(a) linaclotide or pharmaceutically acceptable salts thereof;

(b) $CaCl_2$;

(c) L-Leucine; and

(d) Hydroxypropyl Methylcellulose

wherein linaclotide is present in the pharmaceutical composition in an amount between 100 μg to 600 μg and the molar ratio of Ca^{2+}:leucine:linaclotide is between 5-100:5-50:1.

[00060] In some embodiments, the linaclotide formulation is provided as a capsule or tablet. In some instances, the linaclotide formulation is provided as a capsule. In some specific instances, linaclotide is present in the tablet or capsule in an amount of 133 or 266 μg. In some embodiments, $CaCl_2$ is present in the tablet or capsule in an amount of 1541 μg. In some embodiments, leucine is present in the tablet or capsule in an amount of 687 μg. In some embodiments, hydroxypropyl methylcellulose is present in the tablet or capsule in an amount of 700 μg.

[00061] In some aspects, the method of treating chronic constipation provides an increase in the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week.

[00062] In some embodiments, administering linaclotide according to the invention increases the number of CSBMs by the patient by at least one CSBM per week compared to said patient prior to treatment with linaclotide.

[00063] In still further embodiments, administering linaclotide according to the invention increases the number of CSBMs by the patient to three or greater CSBMs per week.

[00064] In other embodiments, administering linaclotide according to the invention increases the number of CSBMs by the patient by at least one CSBM per week compared to the number of CSBMs by said patient prior to treatment with linaclotide.

[00065] In some embodiments, the method of treating chronic constipation according to the invention results in a 1.5 or greater fold increase of the 12 week CSBM overall responder rate compared to baseline, i.e., prior to treatment with linaclotide. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 2.0 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 2.5 or greater. In still other embodiments, the fold increase of the 12 week CSBM overall responder rate is 3.0 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 3.5 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 4.0 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 4.5 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 5.0 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 5.5 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 6.0 or greater. In other embodiments, the fold increase of the 12 week CSBM overall responder rate is 6.5 or greater.

[00066] In some embodiments, the method of treating chronic constipation according to the invention provides a patient a 1.5 or greater fold increase in that patient's 12 week CSBM

overall response compared to baseline, i.e., prior to treatment with linaclotide. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 2.0 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 2.5 or greater. In still other embodiments, the fold increase in that patient's 12 week CSBM overall response is 3.0 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 3.5 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 4.0 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 4.5 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 5.0 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 5.5 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 6.0 or greater. In other embodiments, the fold increase in that patient's 12 week CSBM overall response is 6.5 or greater.

[00067] In some embodiments, administering linaclotide according to the invention results in a 1.0 or greater increase from baseline in the average weekly CSBMs. In other embodiments, the increase in average weekly CSBMs from baseline is 1.5 or greater. In other embodiments, the increase in average weekly CSBMs from baseline is 2.0 or greater. In other embodiments, the increase in average weekly CSBMs from baseline is 2.5 or greater. In other embodiments, the increase in average weekly CSBMs from baseline is 3.0 or greater.

[00068] In still other embodiments, administering linaclotide according to the invention results in a 1.0 or greater increase from baseline in the weekly CSBMs in at least three-fourths of the weeks for which the therapy is administered. In other embodiments, the invention results in a 1.5 or greater increase in weekly CSBMs from baseline in at least three-fourths of the weeks for which the therapy is administered. In other embodiments, the invention results in a 2.0 or greater increase in weekly CSBMs from baseline in at least three-fourths of the weeks for which the therapy is administered. In other embodiments, the invention results in a 2.5 or greater increase in weekly CSBMs from baseline in at least three-fourths of the weeks for which the therapy is administered. In other embodiments, the invention results in a 3.0 or greater increase in weekly CSBMs from baseline in at least three-fourths of the weeks for which the therapy is administered.

[00069] In some embodiments, administering linaclotide according to the invention results in a 1.0 or greater increase from baseline in the average weekly SBMs. In other embodiments, the increase in average weekly SBMs from baseline is 1.5 or greater. In other embodiments, the increase in average weekly SBMs from baseline is 2.0 or greater. In other

embodiments, the increase in average weekly SBMs from baseline is 2.5 or greater. In other embodiments, the increase in average weekly SBMs from baseline is 3.0 or greater.

[00070] In some embodiments, administering linaclotide to a patient according to the invention results in a mean increase of 1 or greater from baseline in weekly CSBMs. In some embodiments, administering linaclotide to a patient according to the invention results in a mean increase of 2 or greater from baseline in weekly CSBMs.

[00071]

[00072] In some further aspects, the method of treating chronic constipation according to the invention decreases bloating in said patient compared to said patient prior to treatment with linaclotide. In some embodiments, the bloating is abdominal bloating.

[00073] In some embodiments, the method of treating chronic constipation according to the invention decreases abdominal discomfort in the patient compared to said patient prior to treatment with linaclotide.

[00074] In other embodiments, the method of treating chronic constipation according to the invention decreases constipation severity in the patient compared to said patient prior to treatment with linaclotide.

[00075] In yet some further embodiments, the method of treating chronic constipation according to the invention improves stool consistency in the patient compared to said patient prior to treatment with linaclotide.

[00076] In other embodiments, the method of treating chronic constipation according decreases straining during defecation in the patient compared to said patient prior to treatment with linaclotide.

[00077] In other embodiments, the method of treating chronic constipation according to the invention includes improved patient assessment of constipation quality of life as compared to prior treatment with linaclotide.

[00078] In still further embodiments, the method of treating chronic constipation according to the invention improves at least two symptoms in a patient compared to said symptoms prior to linaclotide treatment, wherein the symptoms are selected from an increase in the number of CSBMs per week, a decrease in bloating, a decrease in abdominal discomfort, a decrease in constipation severity, an improvement in stool consistency or a decrease in straining during defecation. For instance, in some embodiments, administering linaclotide further increases the number of CSBMs by the patient to three or greater CSBMs per week.

[00079] In some embodiments, the method of treating a patient with chronic constipation comprises administering a therapeutically effective dose of linaclotide, wherein linaclotide produces a rapid or sustained relief of symptoms associated with chronic constipation.

[00080] In some embodiments, the patient has at least one SBM or CSBM within one week after the administering of a therapeutically effective amount of linaclotide, within 72 hours after the administering of a therapeutically effective amount of linaclotide, within 48 hours after the administering of a therapeutically effective amount of linaclotide, or within 24 hours after the administering of a therapeutically effective amount of linaclotide.

[00081] In some embodiments, the method of treating chronic constipation according to the invention may improve SBM rate, CSBM rate, stool consistency, straining, abdominal discomfort, bloating, constipation severity, or a combination thereof, within one week, 72 hours, 48 hours, 24 hours after the administering of a therapeutically effective amount of linaclotide.

[00082] In another aspect, the method of treating chronic constipation according to the invention includes the absence of a symptom rebound when discontinuing the administration of a therapeutically effective dose of linaclotide.

[00083] In other embodiments, the method of treating chronic constipation according to the invention includes the absence of a symptom rebound when discontinuing the administration of a therapeutically effective dose of linaclotide, wherein said symptoms are selected from a decrease in the rate of CSBMs per week, a decrease in the rate of SBMs per week, an increase in bloating, an increase in abdominal discomfort, an increase in constipation severity, a decrease in stool consistency, or an increase in straining during defecation.

[00084] In further embodiments, discontinuing the administration of linaclotide does not produce a symptom rebound of weekly CSBMs for a patient.

[00085] In other embodiments, discontinuing the administration of linaclotide does not produce a symptom rebound of weekly SBMs for a patient.

[00086] In still other embodiments, discontinuing the administration of linaclotide does produce a symptom rebound of stool consistency for a patient.

[00087] In some embodiments, discontinuing the administration of linaclotide does not produce a symptom rebound of severity of straining during defecation for a patient.

[00088] In some embodiments, discontinuing the administration of linaclotide does not produce a symptom of abdominal discomfort for a patient.

[00089] In other embodiments, discontinuing the administration of linaclotide does not produce a symptom rebound of bloating for a patient.

[00090] In some embodiments, discontinuing the administration of linaclotide does not produce a symptom rebound of constipation severity for a patient.

[00091] In still further embodiments, discontinuing the administration of linaclotide does not produce a symptom rebound for global relief of constipation for a patient.

[00092] In other aspects, the invention provides a method of optimizing the treatment with linaclotide of a patient with chronic constipation. The method includes:

a) administering a first therapeutically effective dose of linaclotide once a day;

b) determining whether the patient develops loose stools or diarrhea after treatment with linaclotide;

c) wherein if the patient develops loose stools or diarrhea after one or more days of said administering, administering a second therapeutically effective dose of linaclotide once a day, wherein said second therapeutically effective dose is lower than said first therapeutically effective dose.

[00093] In some embodiments, the first therapeutically effective dose of linaclotide is 266 μg and the second therapeutically effective dose of linaclotide is 133 μg.

[00094] In some further aspects, the invention provides a method of optimizing the treatment with linaclotide of a patient with chronic constipation. The method includes:

a) administering a first therapeutically effective dose of linaclotide once a day on a first schedule;

b) determining whether the patient develops loose stools or diarrhea after treatment with linaclotide;

c) wherein if the patient develops loose stools or diarrhea after one or more days of said administering, administering a second therapeutically effective dose of linaclotide on a second schedule that is less frequent than the first schedule.

[00095] In some embodiments, the first therapeutically effective dose is the same as the second therapeutically effective dose and the second schedule is less frequent than the first schedule.

[00096] In other embodiments, the first therapeutically effective dose and the second therapeutically effective dose are each 266 μg or are each 133 μg.

[00097] In still other embodiments, the second therapeutically effective dose is lower than the first therapeutically effective dose. For instance, the first therapeutically effective dose of linaclotide is 266 μg and the second therapeutically effective dose of linaclotide is 133 μg and the first schedule and the second schedule are the same.

[00098] In other embodiments, the second schedule that is less frequent than the first schedule.

[00099] In still other embodiments, the first schedule is administration of linaclotide on a daily basis.

[000100]In yet further embodiments, the second schedule is administration of linaclotide every other day, every third day, every fourth day, every fifth day, every sixth day or once weekly.

[000101]In still another aspect, the invention provides a method of optimizing the treatment of a patient with chronic constipation. The method includes:

a) administering a first dose of linaclotide once a day on a first schedule to the patient;

b) determining whether the administering increases the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week; and

c) wherein if the patient has fewer than three CSBMs per week, administering a second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

[000102]In some embodiments, step (b) further requires determining whether the number of CSBMs by the patient increases by at least one CSBM per week compared to the number of CSBMs by said patient prior to treatment with linaclotide; wherein if said number of CSBMs does not increase by at least one CSBM per week, then administering a second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

[000103]In some embodiments, the first dose is lower than the second therapeutically effective dose.

[000104]In specific embodiments, the first dose is 133 μg and the second dose is 266 μg.

[000105]In certain embodiments, the first schedule and the second schedule are the same and is administration of linaclotide on a daily basis.

[000106]In some embodiments, the first dose and the second dose are the same and the second schedule is more frequent than said first schedule. In some instances, the second schedule is administration of linaclotide on a daily basis. In other instances, the first schedule is administration of linaclotide every other day, every third day, every fourth day, every fifth day, every sixth day or once weekly.

[000107]In still further aspects, the invention provides a method of optimizing the treatment of a patient with chronic constipation. The method includes:

(a) administering an amount of linaclotide once a day on a daily basis to the patient; and

(b) determining whether the patient develops loose stools or diarrhea;

wherein the presence of loose stools or diarrhea indicates a need to decrease the amount of linaclotide subsequently administered to said patient and/or decrease the dosing frequency when linaclotide is subsequently administered to said patient.

[000108]In some embodiments, the amount of linaclotide subsequently administered to said patient is decreased.

[000109]In other embodiments, the dosing frequency when linaclotide is subsequently administered is decreased.

[000110]In still further aspects, the invention provides a method of optimizing the treatment of a patient with chronic constipation. The method includes:

(a) administering a first amount of linaclotide once a day at a first frequency to the patient; and

(b) determining whether the administering increases the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week;

wherein the patient having fewer than three CSBMs per week indicates a need to increase second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

[000111]In some embodiments, step (b) further requires determining whether the number of CSBMs by the patient increases by at least one CSBM per week compared to the number of CSBMs by said patient prior to treatment with linaclotide; wherein an increase of less than one CSBM per week indicates a need to increase second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

[000112]In other embodiments, linaclotide can be used to treat bowel symptoms, abdominal symptoms, and rectal symptoms.

[000113]In further embodiments, linaclotide can be used to treat bowel symptoms selected from infrequent bowel movements, hard or lumpy stool, straining, stools too small or too large, unsuccessful attempts to have bowel movements, incomplete bowel movements, long duration of bathroom visit, or digital manipulation.

[000114]In still further embodiments, linaclotide can be used to treat abdominal symptoms selected from abdominal pain, bloating, abdominal discomfort, stomach pain/aches "belly aches", abdominal cramping, feeling of fullness/feeling "stuffed", feeling back-up "loaded" or impacted, gas, trapped gas, backed up gas, gas pockets, passing gas, gas pain, pain in sides or one side, upset stomach, acid stomach, stomach sour, strong odor of gas, or burping/belching.

[000115]In still further embodiments, linaclotide can be used to treat rectal symptoms selected from rectal pain, hemorrhoids, rectal bleeding, rectal tearing, or rectal "burning."

EXAMPLES

Example 1: Preparation of Linaclotide

[000116]Linaclotide as described herein was prepared by solid phase chemical synthesis and natural folding (air oxidation) by Polypeptide Laboratories (Torrance, CA). The oral linaclotide formulation was prepared by Forest Laboratories, Inc. (New York, NY).

Example 2: Linaclotide Formulations

[000117]The formulations used in the invention contain linaclotide or a pharmaceutically acceptable salt of linaclotide. The formulations are stable and have a sufficient shelf life for manufacturing, storing and distributing the drug. For example, the formulations have an expected shelf life of at least 12 months at room temperature storage conditions (e.g., 25°C/60 percent relative humidity (RH)) and up to at least 18 months or 24 months at room temperature storage conditions (e.g., 25°C/60 percent RH). In the formulations, greater than or equal to 95 percent of the original amount of linaclotide in the composition remains after three months when packaged samples are stored at accelerated conditions (40°C/75 percent RH) when assessed in an assay on a weight/weight basis as determined by high pressure liquid chromatography (HPLC) against a linaclotide reference standard.

[000118]The GC-C receptor agonist polypeptide formulations are prepared from a solution, e.g., an aqueous solution ("the coating solution"), comprising: (i) a GC-C receptor agonist polypeptide such as linaclotide or a pharmaceutically acceptable salt thereof; (ii) a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} and Al^{3+} and/or a sterically hindered primary amine (e.g., leucine); and optionally (iii) a pharmaceutically acceptable binder. The GC-C receptor agonist polypeptide formulations can optionally include one or more of a pharmaceutically acceptable glidant, a pharmaceutically acceptable lubricant or a pharmaceutically acceptable additive that acts as both a glidant and lubricant.

[000119]It has been found that a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} and Al^{3+} is useful for suppressing the formation of an oxidation product of the GC-C receptor agonist polypeptide linaclotide during storage. It has also been found that a sterically hindered primary amine is useful for suppressing the formation of a formaldehyde imine adduct of the GC-C receptor agonist polypeptide linaclotide ("formaldehyde imine product") during storage. Thus, the GC-C receptor agonist polypeptide formulations comprising a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+}—e.g., a divalent cation selected

from Zn^{2+}, Mg^{2+} and Ca^{2+}—and/or a sterically hindered primary amine, such as an amino acid, have a sufficient shelf life (as measured by chromatographic purity and/or by a weight/weight assay) for manufacturing, storing and distributing the drug. Further, while the presence of a sterically hindered amine alone can increase the formation of a hydrolysis product of linaclotide during storage, the combination of a sterically hindered primary amine and a cation, e.g., the combination of leucine and Ca^{2+}, suppresses the formation of the hydrolysis product of the GC-C receptor agonist polypeptide as well as the oxidation product of GC-C receptor agonist polypeptide during storage, leading to an even greater overall stability as determined by a weight/weight assay and/or by chromatographic purity.

[000120]GC-C receptor agonist polypeptide formulations are typically produced as follows.

Preparation of the Coating Solution:

[000121]Approximately 8.3 kg of purified water is mixed with hydrochloric acid to create a solution with a pH between 1.5 and 2.0. An oxidation-suppressing cation, if used, is added to the solution in a quantity to provide the desired concentration, and the solution is mixed for sufficient time to produce a clear solution. A sterically hindered primary amine, if used, is added to the solution in a quantity to provide the desired concentration, and the solution is mixed for sufficient time to produce a clear solution. Other additives, such as antioxidants, are then added, if desired. The binder is then added to the solution and the solution is mixed for sufficient time to achieve a clear solution. The pH of the solution is tested, and hydrochloric acid is added if necessary to produce a solution having a pH between 1.5 and 2.0. This is Solution 1. Approximately 8.3 kg of purified water is mixed with hydrochloric acid to create a solution with a pH between 1.5 and 2.0. The desired amount of linaclotide is added to the solution and mixed for 10 to 30 minutes. The pH of the solution is tested, and hydrochloric acid is added if necessary to produce a solution having a pH between 1.5 and 2.0. This is Solution 2. Solution 1 and Solution 2 are then mixed together. The pH of the solution is tested, and hydrochloric acid is added if necessary to produce a solution having a pH between 1.5 and 2.0. This is the coating solution.

Preparation of the Active Beads:

[000122]Approximately 24.19 kg of microcrystalline cellulose beads are added to a Wurster Column of a Glatt GPCG-30 Fluid Bed. The microcrystalline cellulose beads are fluidized and heated to product temperature of 45-47°C. Next, the coating solution is layered to the beads. The product spraying temperature is controlled between 37°C and 47°C by controlling inlet temperature, spray rate, atomization pressure, and air volume. After the

entire coating solution is layered to the beads, the beads are dried with a product drying temperature of 37°C to 47°C. The product of this process is referred to as active beads.

Example 3: Measurement of Linaclotide Content and Purity

[000123]Linaclotide content and purity, as well as measurement of linaclotide-related substances may be determined, for example, by reverse phase gradient liquid chromatography using an Agilent Series 1100 LC System with Chemstation Rev A.09.03 software or equivalent. A YMC Pro™ C18 column (dimensions: 3.0 x 150 mm, 3.5 um, 120 Å; Waters Corp., Milford, MA) or equivalent is used and is maintained at 40°C. Mobile phase A (MPA) consists of water with 0.1% trifluoroacetic acid while mobile phase B (MPB) consists of 95% acetonitrile:5% water with 0.1% trifluoroacetic acid. Elution of linaclotide and its related substances is accomplished with a gradient from 0% to 47% MPB in 28 minutes followed by a ramp to 100% MPB in 4 minutes with a 5 minute hold at 100% MPB to wash the column. Re-equilibration of the column is performed by returning to 0% MPB in 1 minute followed by a 10 minute hold at 100% MPA. The flow rate is 0.6 mL/min and detection is accomplished by UV at 220 nm.

[000124]Samples for analysis are prepared by addition of the contents of linaclotide capsules to 0.1 N HCl to obtain a target concentration of 20 µg linaclotide/mL. A total of 100 µL of this solution is injected onto the column.

[000125]Linaclotide content is measured by determining the linaclotide concentration in the prepared sample against a similarly prepared external linaclotide standard.

[000126]An example of an analysis of linaclotide by HPLC is shown in Figure 13, wherein "Oxidation" refers to the linaclotide oxidation product, "Formaldehyde Imine" refers to the linaclotide formaldehyde imine product and "Hydrolysis" refers to the linaclotide hydrolysis product.

Example 4: Linaclotide Capsule Formulation

[000127]A linaclotide capsule formulation was produced essentially as described in Examples 1 and 2 wherein Table 1 provides the amounts of cation, sterically hindered primary amine, binder, linaclotide and beads, and their theoretical weights (mg/g) and (kg/Batch) for the complete Linaclotide Beads Drug Layer Solution. Table 2 provides the conditions under which the beads were coated. Table 3 provides the ingredients and theoretical weights (mg/g) and (kg/Batch) for the preparation for the Linaclotide Active Beads.

[000128]The Linaclotide active beads were tested for linaclotide content. Based on the assay of the active beads, an appropriate amount of active beads was filled into size 2 hard gelatin capsules, (weight 61 mg), using an MG2 Futura encapsulation machine, to achieve the desired linaclotide concentration. The 150 μg linaclotide capsules contained 56 mg linaclotide beads (600 μg linaclotide/225 mg beads) having an effective linaclotide content of 133 μg, while the 300 μg linaclotide capsules contained 113 mg linaclotide beads (600 μg linaclotide/225 mg beads) having an effective linaclotide content of 266 μg. The linaclotide content can be measured, for example, by using the assay described in Example 3 or by other methods.

Table 1

Ingredients	Function	Theoretical Weight (mg/g)	Theoretical Weight (kg/batch)
Linaclotide	API	2.67	0.067
$CaCl_2 \cdot 2H_2O$, USP, EP, BP, JP	Stabilizer	15.41	0.385
L-Leucine, USP	Stabilizer	6.87	0.172
Hydroxypropyl Methylcellulose, USP (Methocel E5 Premium LV)	Binder	7.00	0.175
Purified Water, USP	--	--	16.666
HCl (36.5-38.0), NF	--	--	0.114

Table 2

Product Spraying Temp (°C)	Inlet Temp (°C)	Spray rate (g/min)	Atomization Pressure (bar)	Process Air Volume (cfm)	Product Drying Temp (°C)
64.9 – 65.1	80	150	2.0	515-564	54.9 – 55.0

Table 3

Ingredients	Function	Theoretical Weight (mg/g)	Theoretical Weight (kg/batch)
Linaclotide Beads Drug Layer Solution	Coating solution	31.95	0.799
Microcrystalline cellulose spheres NF (Celphere CP-305)	Beads	968.05	24.201
Final Total: Linaclotide Beads, 600 μg/225 mg)	Active beads	1000	25.000

Example 5: Administration of Linaclotide for the treatment of chronic constipation.

[000129]Linaclotide Capsules from Example 4 were administered in multicenter, randomized, double-blind, placebo-controlled trials.

Chronic Constipation Trial 1:

[000130]Trial 1 was conducted in 630 patients meeting modified Rome II criteria for chronic constipation. The trial included a two-week pretreatment baseline period and a 12-week treatment period. A diagram of the study design for Trial 2 is given in Figure 1, which is substantially similar to Trial 1 except for the addition of a Randomized Withdrawal period in Trial 2 as described below.

[000131]Pretreatment (Baseline) Period:

[000132]The Pretreatment Period is defined as the 14 to 21 calendar days immediately before starting the trial during which where patients provided information related to their daily bowel habits, daily assessment of the symptom severity, constipation severity, and use of other medicines, laxatives, suppositories, and/or enemas. Patients who satisfy the necessary criteria were entered into the Treatment Period. During the two-week pretreatment period, 72 percent of patients in Trial 1 had no CSBMs. A CSBM is an bowel movement that occurs in the absence of laxative, enema, or suppository usage within the preceding 24 hours that is accompanied by the patient self-reporting a feeling of complete emptying of the bowel.

[000133]Treatment Period:

[000134]The Treatment Period began with randomization and lasted for 12 weeks. Patients were randomized to treatment with 133 μg linaclotide, 266 μg linaclotide, or placebo (1:1:1), taken once daily in the morning. Patients continued to provide their daily assessments such as their daily bowel habit assessments and daily patient symptom severity assessments.

[000135]The primary efficacy endpoint was a 12-week CSBM overall responder, a patient who had a three or more CSBMs per week and an increase of at least one CSBM per week over baseline for at least nine of the 12 weeks of the treatment period.

[000136]During the two-week pretreatment period, 72 percent of patients had no CSBMs.

[000137]Results of Trial 1:

[000138]A significantly greater percentage of patients treated with linaclotide reported a SBM or CSBM within 24 hours of treatment than patients in the placebo group (Figures 12a and 12b). A total of 64.3 percent of patients in the 133 μg linaclotide treatment group reported at least one SBM within 24 hours of treatment ($p<0.0001$), and 60.4 percent reported at least one SBM within 24 hours of treatment in the 266 μg group ($p<0.0001$), versus 39.1

percent reporting at least one SBM in the placebo group. A total of 28.2 percent of patients in the 133 µg linaclotide treatment group reported at least one CSBM within 24 hours of treatment ($p<0.001$), and 29.7 percent reported at least one CSBM within 24 hours of treatment in the 266 µg group ($p<0.0001$), versus 13.5 percent reporting at least one SBM in the placebo group.

[000139] After one week, statistically significant improvements from baseline to Week 1 for the 133 µg and 266 µg linaclotide groups versus the change over baseline in the placebo were observed for SBM rate, CSBM rate, stool consistency, constipation severity, and straining (all at $p<0.0001$); bloating ($p<0.01$ for 133 µg, $p<0.0001$ for 266 µg), and abdominal discomfort ($p<0.001$ for 133 µg, $p<0.0001$ for 266 µg). The mean changes from baseline for each variable in each treatment group are provided in Table 4, below.

Table 4: Week 1 Mean Change from Baseline in CC symptoms, by Dose

	Placebo			133 µg Linaclotide			266 µg Linaclotide		
	Trial 2 (n=209)	**Trial 1 (n=215)**	**Pooled (n=424)**	**Trial 2 (n=217)**	**Trial 1 (n=213)**	**Pooled (n=430)**	**Trial 2 (n=216)**	**Trial 1 (n=202)**	**Pooled (n=418)**
SBM rate	1.11	1.19	1.31	3.59***	4.09***	3.96***	3.61***	4.09***	4.01***
CSBM rate	0.24	0.45	0.48	1.89***	1.94***	2.02**	2.02***	2.63***	2.42**
Stool Consistency[a]	0.33	0.38	0.39	1.75***	1.79***	1.78***	1.81***	1.96***	1.87***
Straining[b]	-0.28	-0.38	-0.33	-0.99***	-1.04***	-1.02***	-1.06***	-1.10***	-1.14***
Abdominal discomfort[c]	-0.13	-0.06	-0.12	-0.23	-0.27**	-0.26***	-0.21	-0.28***	-0.26***
Bloating[c]	-0.13	-0.14	-0.13	-0.32**	-0.31*	-0.31***	-0.27*	-0.36***	-0.31***
Constipation severity[c]	-0.22	-0.13	-0.23	-0.80***	-0.78***	-0.82***	-0.76***	-0.81***	-0.85***

*P<0.01, **P<0.001, *** P<0.0001 vs placebo
[a] 7-point scale (BSFS): 1 = separate hard lumps like nuts; 7 = watery, no solid pieces.
[b] 5-point scale: 1 = none; 5 = an extreme amount.
[c] 5-point scale: 1 = none; 5 = very severe.

[000140] The 12-week CSBM overall responder rate was 16.0 percent in the 133 µg linaclotide group ($p=0.0012$) and 21.3 percent in the 266 µg linaclotide group ($p\leq0.0001$), a numerical increase of 2.6 and 3.5 fold, respectively, as compared to 6.0 percent in the placebo group. A total of 16.0 percent ($p=0.0012$) of patients receiving 133 µg and 21.8 percent ($p\leq0.0001$) of patients receiving 266 µg of linaclotide experienced ≥3 weekly CSBMs in at

least nine out of 12 weeks as compared to 6.0 percent of patients receiving placebo. In addition 31.0 percent ($p \leq 0.0001$) of patients receiving 133 μg and 40.1 percent ($p \leq 0.0001$) of patients receiving 266 μg of linaclotide achieved an increase of ≥1 from baseline in weekly CSBMs in at least nine out of 12 weeks as compared to 13.0 percent of patients receiving placebo.

[000141] In at least six out of 12 weeks, 47.4 percent ($p \leq 0.001$) of patients receiving 133 μg and 51.0 percent ($p \leq 0.001$) of patients receiving 266 μg of linaclotide achieved an increase of ≥1 from baseline in weekly CSBMs as compared to 26.5 percent of patients receiving placebo (Figure 11).

[000142]Linaclotide-treated patients demonstrated a significant increase in average weekly CSBMs from baseline (0.6 for placebo; 2.0 for 133 μg, $p \leq 0.0001$; 2.7 for 266 μg, $p \leq 0.0001$). Linaclotide-treated patients demonstrated a significant increase in average weekly SBMs from baseline (1.1 for placebo; 3.4 for 133 μg, $p \leq 0.0001$; 3.7 for 266 μg, $p \leq 0.0001$) (Figure 4).

[000143] The patients in Trial 1 also exhibited qualitative improvements for the 12 week overall mean changes for linaclotide-treated patients versus the placebo-treated patients (Figures 5-10). These patients exhibited statistically significant improvements in scores for: stool consistency for both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$) (Figure 5); severity of straining for both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$) (Figure 6); bloating for both doses of 133 μg ($p \leq 0.001$) and 266 μg ($p \leq 0.0001$) (Figure 7); abdominal discomfort across for doses of 133 μg ($p \leq 0.001$) and 266 μg ($p \leq 0.0001$) (Figure 8); constipation severity for both doses of 133 μg ($p \leq 0.001$) and 266 μg ($p \leq 0.0001$) (Figure 9); and PAC-QOL overall assessments at both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$) (Figure 10).

[000144] Patients in Trial 1 receiving linaclotide treatment also had significant qualitative improvements in PAC-QOL subscales scores for Satisfaction, Physical Discomfort, and Worries/Concerns Subscale. These patients exhibited statistically significant improvements for linaclotide versus placebo for subscale scores for (i) Satisfaction across both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$), (ii) Physical Discomfort across both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$), and (iii) Worries/Concerns across both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$).

<u>Chronic Constipation Trial 2:</u>

[000145]Trial 2 was conducted in 642 patients and was identical to Trial 1 except that Trial 2 also included a four-week Randomized Withdrawal Period, defined below. The experimental

design for Trial 2 is given in Figure 1. During the two-week pretreatment (baseline) period, 68 percent of patients in Trial 2 had no CSBMs.

[000146]Results of Trial 2:

[000147]A significantly greater percentage of patients treated with linaclotide reported a SBM or CSBM within 24 hours of treatment than patients in the placebo group (Figures 12a and 12b). A total of 70.0 percent of patients in the 133 μg linaclotide treatment group reported at least one SBM within 24 hours of treatment ($p<0.0001$), and 54.6 percent reported at least one SBM within 24 hours of treatment in the 266 μg group ($p<0.01$), versus 39.7 percent reporting at least one SBM in the placebo group. A total of 33.2 percent of patients in the 133 μg linaclotide treatment group reported at least one CSBM within 24 hours of treatment ($p<0.0001$), and 26.9 percent reported at least one CSBM within 24 hours of treatment in the 266 μg group ($p<0.0001$), versus 11.0 percent reporting at least one SBM in the placebo group.

[000148]After one week, statistically significant improvements from baseline to Week 1 for the 133 μg and 266 μg linaclotide groups versus the change over baseline in the placebo were observed for SBM rate, CSBM rate, stool consistency, constipation severity, and straining (all at $p<0.0001$); as well as bloating ($p<0.001$ for 133 μg, $p<0.01$ for 266 μg). Statistically significant improvement were seen in abdominal discomfort in week 2 of study 2 ($p<0.01$). The mean changes from baseline for each variable in each treatment group are provided in Table 4, above.

[000149]The 12-week CSBM overall responder rate was 21.2 percent in the 133 μg linaclotide group ($p\leq0.0001$) and 19.4 percent in the 266 μg linaclotide group ($p\leq0.0001$), a numerical increase of 6.3 and 5.8 fold, respectively, as compared to 3.3 percent in the placebo group. A total of 21.7 percent ($p\leq0.0001$) of patients receiving 133 μg and 19.4 percent ($p\leq0.0001$) of patients receiving 266 μg of linaclotide experienced ≥3 weekly CSBMs in at least nine out of 12 weeks as compared to 3.8 percent of patients receiving placebo. In addition 39.2 percent ($p\leq0.0001$) of patients receiving 133 μg and 37.0 percent ($p\leq0.0001$) of patients receiving 266 μg of linaclotide achieved an increase of ≥1 from baseline in weekly CSBMs in at least nine out of 12 weeks as compared to 11.0 percent of patients receiving placebo.

[000150]In at least six out of 12 weeks 56.7 percent ($p\leq0.001$) of patients receiving 133 μg and 50.5 percent ($p\leq0.001$) of patients receiving 266 μg of linaclotide achieved an increase of ≥1 from baseline in weekly CSBMs as compared to 24.4 percent of patients receiving placebo (Figure 11).

[000151]Linaclotide-treated patients demonstrated a significant increase in average weekly CSBMs from baseline (0.5 for placebo; 1.9 for 133 μg, $p \leq 0.0001$; 2.0 for 266 μg, $p \leq 0.0001$). Linaclotide-treated patients demonstrated a significant increase in average weekly SBMs from baseline (1.1 for placebo; 3.0 for 133 μg, $p \leq 0.0001$; 3.0 for 266 μg, $p \leq 0.0001$) (Figure 4).

[000152]The patients in Trial 2 also exhibited qualitative improvements in overall change for bloating ($p \leq 0.01$ and $p \leq 0.001$), abdominal discomfort ($p \leq 0.01$ and $p \leq 0.001$), overall stool consistency ($p \leq 0.001$), overall severity in straining ($p \leq 0.001$), and constipation severity ($p \leq 0.001$), which were statistically significant for linaclotide versus placebo for both doses.

[000153]The patients in Trial 2 also exhibited qualitative improvements for the 12 week overall mean changes for linaclotide-treated patients versus the placebo-treated patients (Figures 5-10). These patients exhibited statistically significant improvements in scores for: stool consistency for both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$); severity of straining for both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$); bloating for both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.01$); abdominal discomfort across for doses of 133 μg ($p \leq 0.001$) and 266 μg ($p \leq 0.01$); overall constipation severity for both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$); and PAC-QOL overall assessments at both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$).

[000154] Patients in Trial 1 receiving linaclotide treatment also had significant qualitative improvements in PAC-QOL subscales scores for Satisfaction, Physical Discomfort, and Worries/Concerns Subscale. These patients exhibited statistically significant improvements for linaclotide versus placebo for subscale scores for (i) Satisfaction across both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$), (ii) Physical Discomfort across both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$), and (iii) Worries/Concerns across both doses of 133 μg ($p \leq 0.0001$) and 266 μg ($p \leq 0.0001$).

[000155]<u>Randomized Withdrawal Period:</u>

[000156]The Randomized Withdrawal (RW) Period is defined as the 4 weeks immediately following the Treatment Period. The beginning of the RW Period coincides with the end of the Treatment Period. Patients who were randomized to linaclotide in the Treatment Period and complete the 12 weeks of the Treatment Period were randomized to treatment with linaclotide or placebo in the RW Period. Patients who were randomized to placebo in the Treatment Period and complete the 12 weeks of the Treatment Period received 133μg or 266μg linaclotide in the RW Period.

[000157] The results from the Randomized Withdrawal Period are shown below in Table 5 and Figures 2 and 3 and demonstrate that for (i) patients administered linaclotide for the 12 week period and re-randomized to placebo during the 4 week withdrawal period there were no decreases in CSBM (Figure 2) or SBM rates (Figure 3) below the baseline rates for these patients, and (ii) patients administered placebo for the 12 week period and re-randomized to linaclotide during the 4 week withdrawal period exhibited CSBM/SBM rates and qualitative improvements in other bowel and abdominal symptoms similar to the rates and improvements experienced by patients treated for 12 weeks with linaclotide (see Figures 2 and 3).

[000158] The results from Randomized Withdrawal Period additionally demonstrate that patients initiating linaclotide treatment had marked improvement in CC symptoms. There was no evidence of rebound of CC symptoms or increase in the frequencies of adverse events following discontinuing of linaclotide treatment. The incidence of adverse events in patients initiating linaclotide treatment was similar to the incidence in those receiving linaclotide during the first 4 weeks of the Treatment Period. Patients continuing linaclotide treatment showed sustained improvements in bowel and abdominal symptoms and global assessments.

Table 5: Change From Baseline in Bowel and Abdominal Symptoms (RW Period, by Treatment Sequence; RW Population)

Efficacy Parameter	Baseline Value Mean (SD)	RW: Placebo Mean (95% CI)		RW: Linaclotide Mean (95% CI)		
	All Patients (N=538)	133 µg/ Placebo (n=95)	266 µg/ Placebo (n=86)	133 µg/ 133 µg (n=90)	266 µg/ 266 µg (n=90)	Placebo/ 266 µg (n=177)
Weekly CSBM Rate	0.3 (0.6)	1.0 (0.6, 1.3)	0.9 (0.5, 1.4)	2.1 (1.5, 2.8)	2.2 (1.6, 2.8)	2.1 (1.7, 2.5)
Weekly SBM Rate	2.0 (1.6)	1.2 (0.6, 1.8)	1.3 (0.6, 2.0)	3.0 (2.3, 3.6)	2.5 (1.8, 3.2)	3.7 (3.1, 4.3)
Stool Consistency (BSFS)	2.4 (1.0)	1.0 (0.7, 1.2)	0.8 (0.5, 1.1)	1.9 (1.6, 2.3)	1.6 (1.3, 1.9)	1.9 (1.6, 2.1)
Straining	3.2 (0.9)	-0.8 (-1.0, -0.7)	-0.8 (-1.1, -0.5)	-1.1 (-1.3, -0.9)	-1.3 (-1.5, -1.1)	-1.2 (-1.3, -1.0)
Abdominal Discomfort	2.5 (0.8)	-0.4 (-0.6, -0.3)	-0.4 (-0.6, -0.2)	-0.5 (-0.7, -0.4)	-0.7 (-0.8, -0.5)	-0.5 (-0.6, -0.4)
Bloating	2.8 (0.9)	-0.4 (-0.5, -0.2)	-0.2 (-0.4, -0.3)	-0.4 (-0.6, -0.3)	-0.6 (-0.7, -0.4)	-0.5 (-0.6, -0.3)
Constipation Severity	3.3 (0.7)	-0.5 (-0.7, -0.3)	-0.5 (-0.7, -0.3)	-0.9 (-1.1, -0.7)	-0.9 (-1.2, -0.7)	-1.0 (-1.1, -0.9)
Global Relief of Constipation Symptoms	4.0 (0.6)	-0.7 (-1.0, -0.5)	-0.8 (-1.1, -0.6)	-1.3 -1.5, -1.1)	-1.3 (-1.6, -1.1)	-1.3 (-1.6, -1.1)

CI = confidence interval; SD = std. deviation

[000159] For both trial 1 and 2, the most common adverse events in linaclotide-treated patients were diarrhea, flatulence, and abdominal pain. Overall rates of discontinuation due to adverse events were 7.4 percent for linaclotide and 4.2 percent for placebo.

OTHER EMBODIMENTS

[000160] All publications and patents referred to in this disclosure are incorporated herein by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Should the meaning of the terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms used in this disclosure, the meaning of the terms in this disclosure are intended to be controlling. Furthermore, the foregoing discussion discloses and describes merely exemplary embodiments of the present invention. One skilled in the art will readily recognize from such discussion and from the accompanying drawings and claims, that various changes, modifications and variations can be made therein without departing from the spirit and scope of the invention as defined in the following claims.

WHAT IS CLAIMED IS:

1. A method of treating a patient with chronic constipation, comprising administering a therapeutically effective dose of linaclotide once a day.

2. The method according to claim 1, wherein the therapeutically effective dose is administered once a day in the morning.

3. The method according to claim 2, wherein the therapeutically effective dose is administered at least 30 minutes before ingestion of food.

4. The method according to any one of claims 1-3, wherein the therapeutically effective dose is 100 to 600 μg linaclotide.

5. The method according to claim 4, wherein the therapeutically effective dose is 133 μg or 266 μg linaclotide.

6. The method according to any one of claims 1-5, wherein the linaclotide is administered for a period of greater than four weeks.

7. The method according to claim 6, wherein the linaclotide is administered for a period of at least 12 weeks.

8. The method according to either of claims 6 or 7, wherein the linaclotide is administered each day of the week.

9. The method according to either of claims 6 or 7, wherein the linaclotide is administered at least once a week, at least twice a week, at least three times a week, at least four times a week, at least five times a week or at least six times a week.

10. The method according to any one of claims 1-9, wherein the linaclotide is provided in a formulation comprising

(a) linaclotide or pharmaceutically acceptable salts thereof;

(b) $CaCl_2$;

(c) L-Leucine; and

(d) Hydroxypropyl Methylcellulose

wherein linaclotide is present in the pharmaceutical composition in an amount between 100μg to 600μg and the molar ratio of Ca^{2+}:leucine:linaclotide is between 5-100:5-50:1.

11. The method of claim 10, wherein the pharmaceutical composition contains 133 μg of linaclotide.

12. The method of claim 10, wherein the pharmaceutical composition contains 266 μg of linaclotide.

13. The method according to any one of claims 10-12, wherein the linaclotide is provided as a capsule or tablet.

14. The method according to claim 13, wherein the linaclotide is provided as a capsule.

15. The method according to any one of claims 1-14, wherein the administering increases the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week.

16. The method according to any one of claims 1-14, wherein the administering increases the number of CSBMs by the patient by at least one CSBM per week compared to said patient prior to treatment with linaclotide.

17. The method according to any one of claims 1-14, wherein the administering increases the number of CSBMs by the patient to three or greater CSBMs per week and increases the number of CSBMs by the patient by at least one CSBM per week compared to the number of CSBMs by said patient prior to treatment with linaclotide.

18. The method according to any one of claims 1-17, wherein the administering decreases bloating in said patient compared to said patient prior to treatment with linaclotide.

19. The method according to claim 18, wherein said bloating is abdominal bloating.

20. The method according to any one of claims 1-19, wherein the administering decreases abdominal discomfort in said patient compared to said patient prior to treatment with linaclotide.

21. The method according to any one of claims 1-20, wherein the administering decreases constipation severity in said patient compared to said patient prior to treatment with linaclotide.

22. The method according to any one of claims 1-21, wherein the administering improves stool consistency in said patient compared to said patient prior to treatment with linaclotide.

23. The method according to any one of claims 1-22, wherein the administering decreases straining during defecation in said patient compared to said patient prior to treatment with linaclotide.

24. The method according to any one of claims 1-23, wherein the administering improves patient assessment of constipation quality of life compared to the prior treatment with linaclotide.

25. The method according to any one of claims 1-24, wherein the administering improves at least two symptoms in a patient compared to said symptoms prior to linaclotide treatment, wherein the symptoms are selected from an increase in the number of CSBMs per week, a decrease in bloating, a decrease in abdominal discomfort, a decrease in constipation severity, an improvement in stool consistency or a decrease in straining during defecation.

26. The method according to claim 25, wherein said administering further increases the number of CSBMs by the patient to three or greater CSBMs per week.

27. The method according to any one of claims 1-26, wherein discontinuing the administration of a therapeutically effective dose of linaclotide does not produce a rebound of the symptoms in said patient.

28. The method according to any one of claims 1-27, wherein discontinuing the administration of a therapeutically effective dose of linaclotide does not produce a symptom rebound for the patient, wherein said symptom is selected from a decrease in the number of

CSBMs per week, a decrease in the number of SBMs per week, an increase in bloating, an increase in abdominal discomfort, an increase in constipation severity, a decrease in stool consistency, or an increase in straining during defecation.

29. The method according to any one of claims 1-28, wherein discontinuing the administration of linaclotide does not produce a symptom rebound of weekly CSBMs for said patient.

30. The method according to any one of claims 1-29, wherein discontinuing the administration of linaclotide does not produce a symptom rebound of weekly SBMs for said patient.

31. The method according to any one of claims 1-30, wherein discontinuing the administration of linaclotide does not produce a symptom rebound of stool consistency for said patient.

32. The method according to any one of claims 1-31, wherein discontinuing the administration of linaclotide does not produce a symptom rebound of straining during defecation for said patient.

33. The method according to any one of claims 1-32, wherein discontinuing the administration of linaclotide does not produce a symptom rebound of abdominal discomfort for said patient.

34. The method according to any one of claims 1-33, wherein discontinuing the administration of linaclotide does not produce a symptom rebound of bloating for said patient.

35. The method according to any one of claims 1-34, wherein discontinuing the administration of linaclotide does not produce a symptom rebound of constipation severity for said patient.

36. The method according to any one of claims 1-35, wherein discontinuing the administration of linaclotide does not produce a symptom rebound for global relief of constipation for said patient.

37. A method of optimizing the treatment with linaclotide of a patient with chronic constipation, comprising

a) administering a first therapeutically effective dose of linaclotide once a day;

b) determining whether the patient develops loose stools or diarrhea after treatment with linaclotide;

c) wherein if the patient develops loose stools or diarrhea after one or more days of said administering, administering a second therapeutically effective dose of linaclotide once a day, wherein said second therapeutically effective dose is lower than said first therapeutically effective dose.

38. The method according to claim 37, wherein the first therapeutically effective dose of linaclotide is 266 μg and the second therapeutically effective dose of linaclotide is 133 μg.

39. A method of optimizing the treatment with linaclotide of a patient with chronic constipation, comprising

a) administering a first therapeutically effective dose of linaclotide once a day on a first schedule;

b) determining whether the patient develops loose stools or diarrhea after treatment with linaclotide;

c) wherein if the patient develops loose stools or diarrhea after one or more days of said administering, administering a second therapeutically effective dose of linaclotide on a second schedule that is less frequent than the first schedule.

40. The method according to claim 39, wherein the first therapeutically effective dose is the same as the second therapeutically effective dose and the second schedule is less frequent than the first schedule.

41. The method according to claim 40, wherein the first therapeutically effective dose and the second therapeutically effective dose are each 266 μg or are each 133 μg.

42. The method according to claim 39, wherein the second therapeutically effective dose is lower than the first therapeutically effective dose.

43. The method according to claim 42, wherein the first therapeutically effective dose of linaclotide is 266 μg and the second therapeutically effective dose of linaclotide is 133 μg and the first schedule and the second schedule are the same.

44. The method according to either of claims 39 or 42, wherein the second schedule that is less frequent than the first schedule.

45. The method according to any one of claims 39-42 or 44, wherein said first schedule is administration of linaclotide on a daily basis.

46. The method according to claim 45, wherein said second schedule is administration of linaclotide every other day, every third day, every fourth day, every fifth day, every sixth day or once weekly.

47. A method of optimizing the treatment of a patient with chronic constipation, comprising:

a) administering a first dose of linaclotide once a day on a first schedule to the patient; and

b) determining whether the administering increases the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week;

c) wherein if the patient has fewer than three CSBMs per week, administering a second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

48. The method according to claim 47, wherein step (b) further requires determining whether the number of CSBMs by the patient increases by at least one CSBM per week compared to the number of CSBMs by said patient prior to treatment with linaclotide;

wherein if said number of CSBMs does not increase by at least one CSBM per week, then administering a second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

49. The method according to either of claims 47 or 48, wherein the first dose is lower than the second therapeutically effective dose.

50. The method according to claim 49, wherein the first dose is 133 μg and the second dose is 266 μg.

51. The method according to claim either of claims 49 or 50, wherein the first schedule and the second schedule are the same and is administration of linaclotide on a daily basis.

52. The method according to either of claims 47 or 48, wherein the first dose and the second dose are the same and said second schedule is more frequent than said first schedule.

53. The method according to claim 52, wherein said second schedule is administration of linaclotide on a daily basis.

54. The method according to claim 53, wherein said first schedule is administration of linaclotide every other day, every third day, every fourth day, every fifth day, every sixth day or once weekly.

55. A method of optimizing the treatment of a patient with chronic constipation, comprising:

(a) administering an amount of linaclotide once a day on a daily basis to the patient; and

(b) determining whether the patient develops loose stools or diarrhea;

wherein the presence of loose stools or diarrhea indicates a need to decrease the amount of linaclotide subsequently administered to said patient and/or decrease the dosing frequency when linaclotide is subsequently administered to said patient.

56. The method according to claim 55, wherein the amount of linaclotide subsequently administered to said patient is decreased.

57. The method according to claim 55, wherein the dosing frequency when linaclotide is subsequently administered is decreased.

58. A method of optimizing the treatment of a patient with chronic constipation, comprising:

(a) administering a first amount of linaclotide once a day at a first frequency to the patient; and

(b) determining whether the administering increases the number of complete spontaneous bowel movements (CSBMs) by the patient to three or greater CSBMs per week;

wherein the patient having fewer than three CSBMs per week indicates a need to increase second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

59. The method according to claim 58, wherein step (b) further requires determining whether the number of CSBMs by the patient increases by at least one CSBM per week compared to the number of CSBMs by said patient prior to treatment with linaclotide;

wherein an increase of less than one CSBM per week indicates a need to increase second dose of linaclotide once a day that is higher than said first dose of linaclotide and/or administering said linaclotide on a second schedule that is more frequent than said first schedule.

60. A method of treating a patient with chronic constipation, comprising administering a therapeutically effective dose of a GC-C agonist and wherein discontinuing the administration of a therapeutically effective dose of a GC-C does not produce a chronic constipation symptom rebound for said patient.

61. The method according to claim 60, wherein the linaclotide is administered for a period of at least 6 weeks.

62. The method according to any of claims 1-36, wherein the patient has at least one SBM or CSBM within one week after the administering of a therapeutically effective amount of linaclotide.

63. The method according to claim 62, wherein the patient has at least one SBM or CSBM within 72 hours after the administering of a therapeutically effective amount of linaclotide.

64. The method according to claim 63, wherein the patient has at least one SBM or CSBM within 48 hours after the administering of a therapeutically effective amount of linaclotide.

65. The method according to claim 64, wherein the patient has at least one SBM or CSBM within 24 hours after the administering of a therapeutically effective amount of linaclotide.

66. The method according to any of claims 1-36, wherein the patient exhibits an improvement in any of SBM rate, CSBM rate, stool consistency, straining , abdominal discomfort, bloating, constipation severity, or a combination thereof within one week after the administering of a therapeutically effective amount of linaclotide.

67. The method according to claim 66, wherein the patient exhibits an improvement in any of SBM rate, CSBM rate, stool consistency, straining, abdominal discomfort, bloating, constipation severity, or a combination thereof within 72 hours after the administering of a therapeutically effective amount of linaclotide.

68. The method according to claim 67, wherein the patient exhibits an improvement in any of SBM rate, CSBM rate, stool consistency, straining, abdominal discomfort, bloating, constipation severity, or a combination thereof within 48 hours after the administering of a therapeutically effective amount of linaclotide.

69. The method according to claim 68, wherein the patient exhibits an improvement in any of SBM rate, CSBM rate, stool consistency, straining, abdominal discomfort, bloating, constipation severity, or a combination thereof within 24 hours after the administering of a therapeutically effective amount of linaclotide.

70. A method of treating a patient with chronic constipation, comprising administering a therapeutically effective dose of a GC-C agonist, wherein the GC-C agonist produces a rapid or sustained relief of symptoms associated with chronic constipation.

71. The method according to claim 70, wherein the rapid relief occurs within one week.

72. The method according to claim 71, wherein the rapid relief occurs within 72 hours.

73. The method according to claim 72, wherein the rapid relief occurs within 48 hours.

74. The method according to claim 73, wherein the rapid relief occurs within 24 hours.

75. The method according to claim 70, wherein the sustained relief occurs for at least 16 weeks.

76. The method according to claim 70, wherein the sustained relief occurs for at least 9 weeks out of 16 weeks.

77. The method according to claim 70, wherein the sustained relief occurs for at least 6 weeks out of 16 weeks.

78. The method according to claim 70, wherein the sustained relief occurs for at least 3 weeks out of 4 weeks.

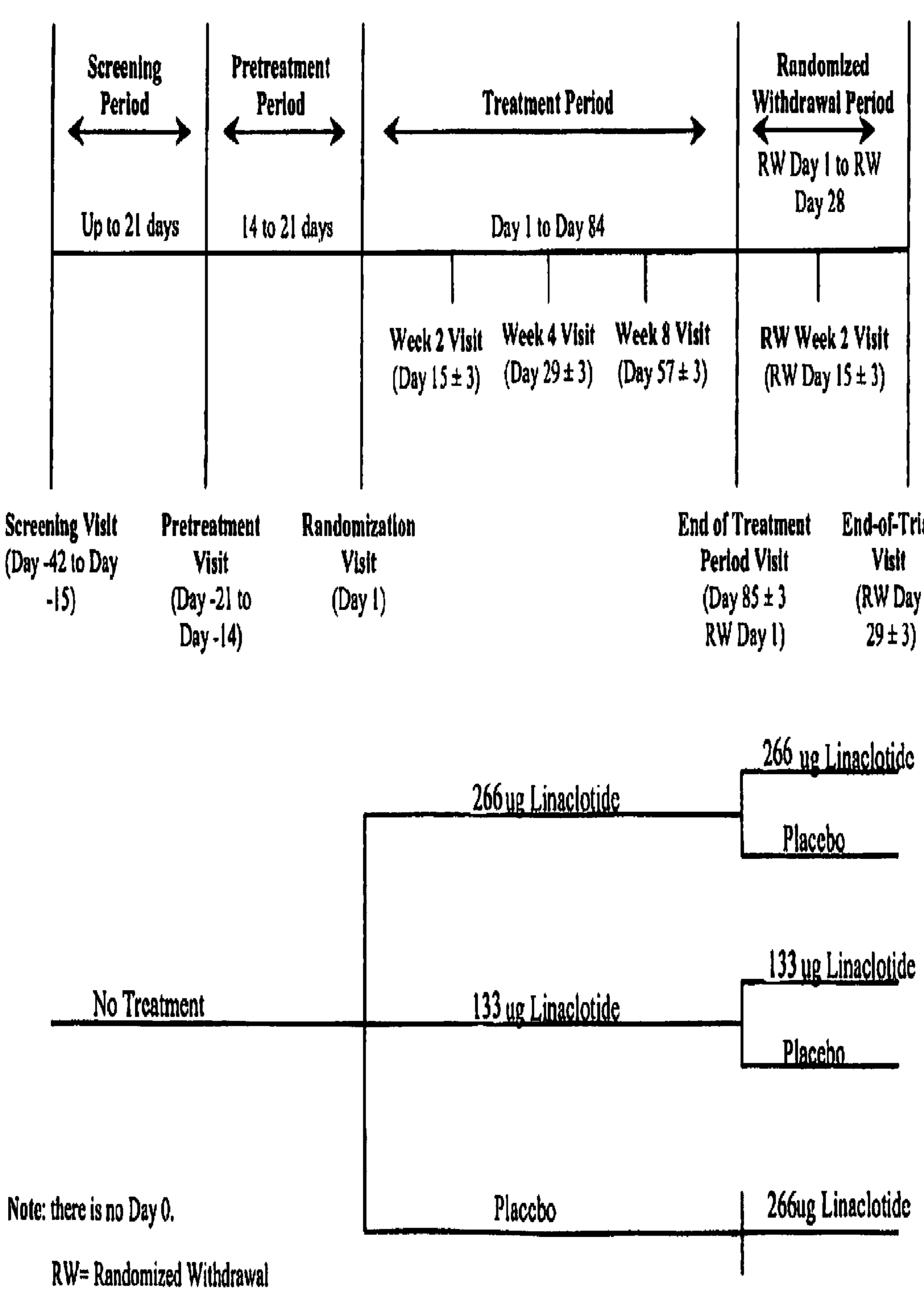
79. The method according to claim 70, wherein the sustained relief occurs for at least 1 week out of 2 weeks.

80. The method according to claim 70, wherein the sustained relief occurs for at least 1 week.

81. The method according to claim 70, wherein the sustained relief occurs for at least 2 weeks.

82. The method according to any one of claims 70-81, wherein the GC-C agonist is linaclotide.

FIGURE 1



REPLACEMENT SHEET 1/14

FIGURE 2

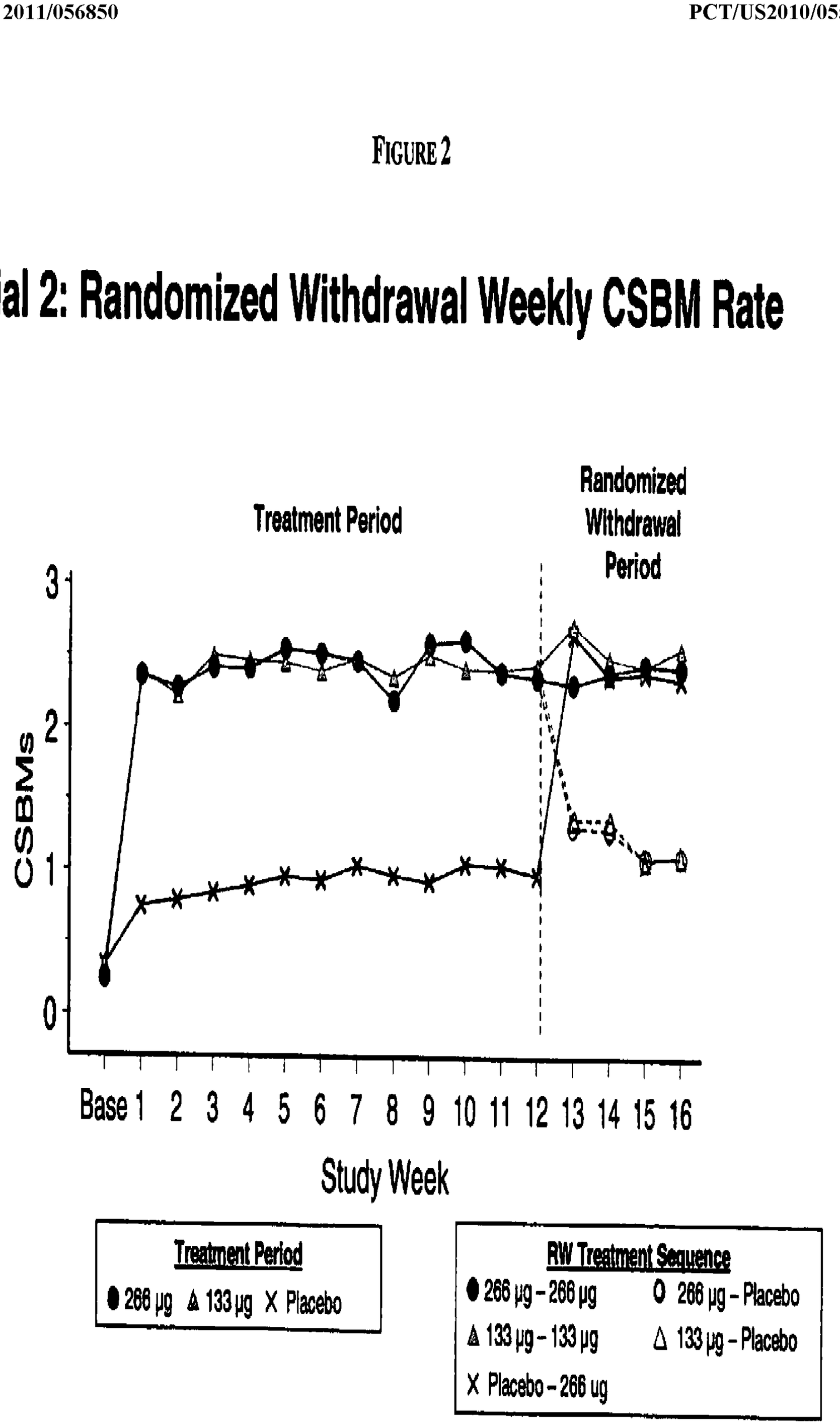
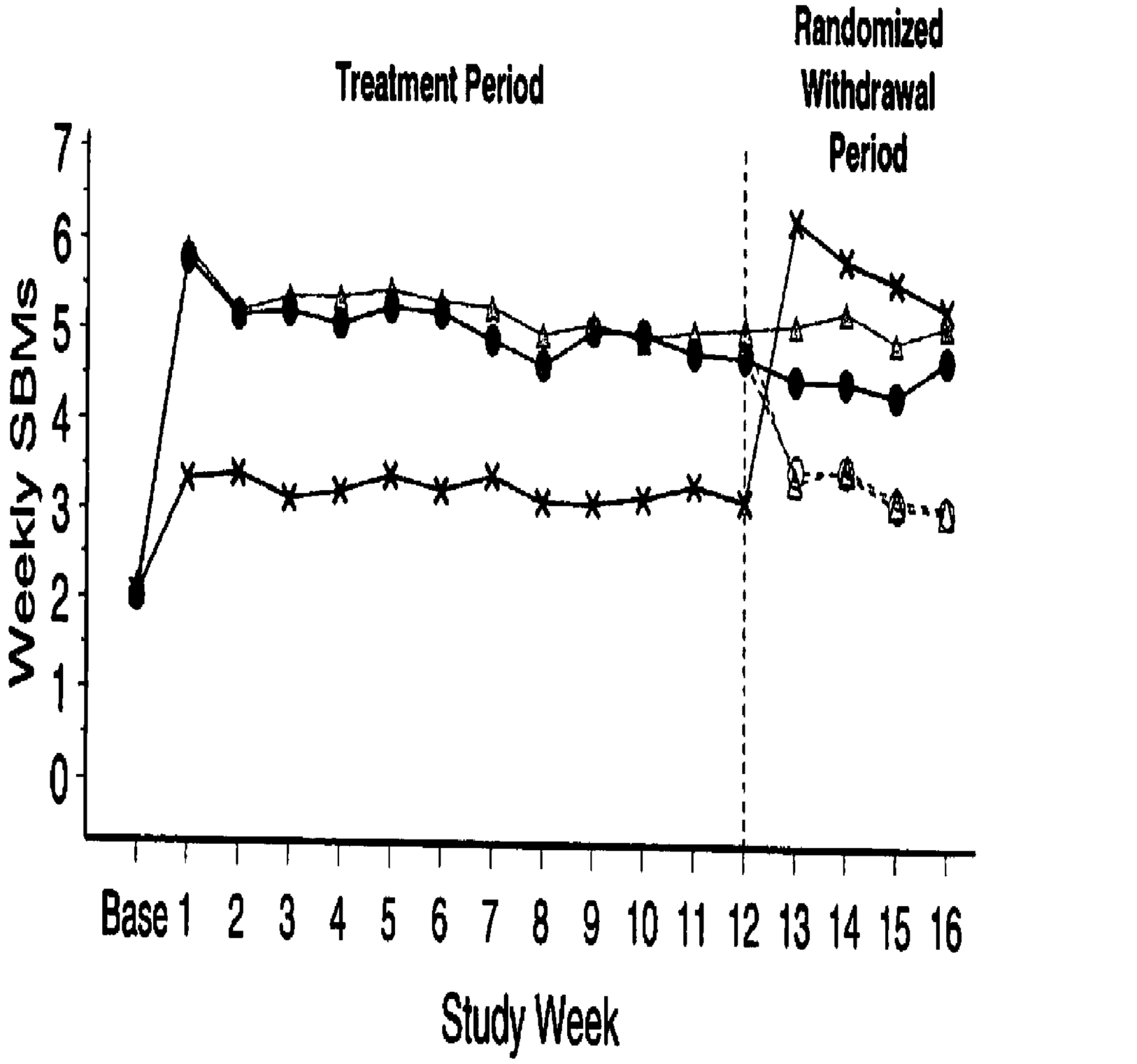

Trial 2: Randomized Withdrawal Weekly CSBM Rate
Treatment Period
Randomized Withdrawal Period
CSBMs
3
2
1
0
Base 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Study Week
Treatment Period
266 µg 133 µg Placebo
RW Treatment Sequence
266 µg – 266 µg
266 µg – Placebo
133 µg – 133 µg
133 µg – Placebo
Placebo – 266 ug
REPLACEMENT SHEET 2/14

FIGURE 3

Trial 2: Randomized Withdrawal Weekly SBM Rate



REPLACEMENT SHEET
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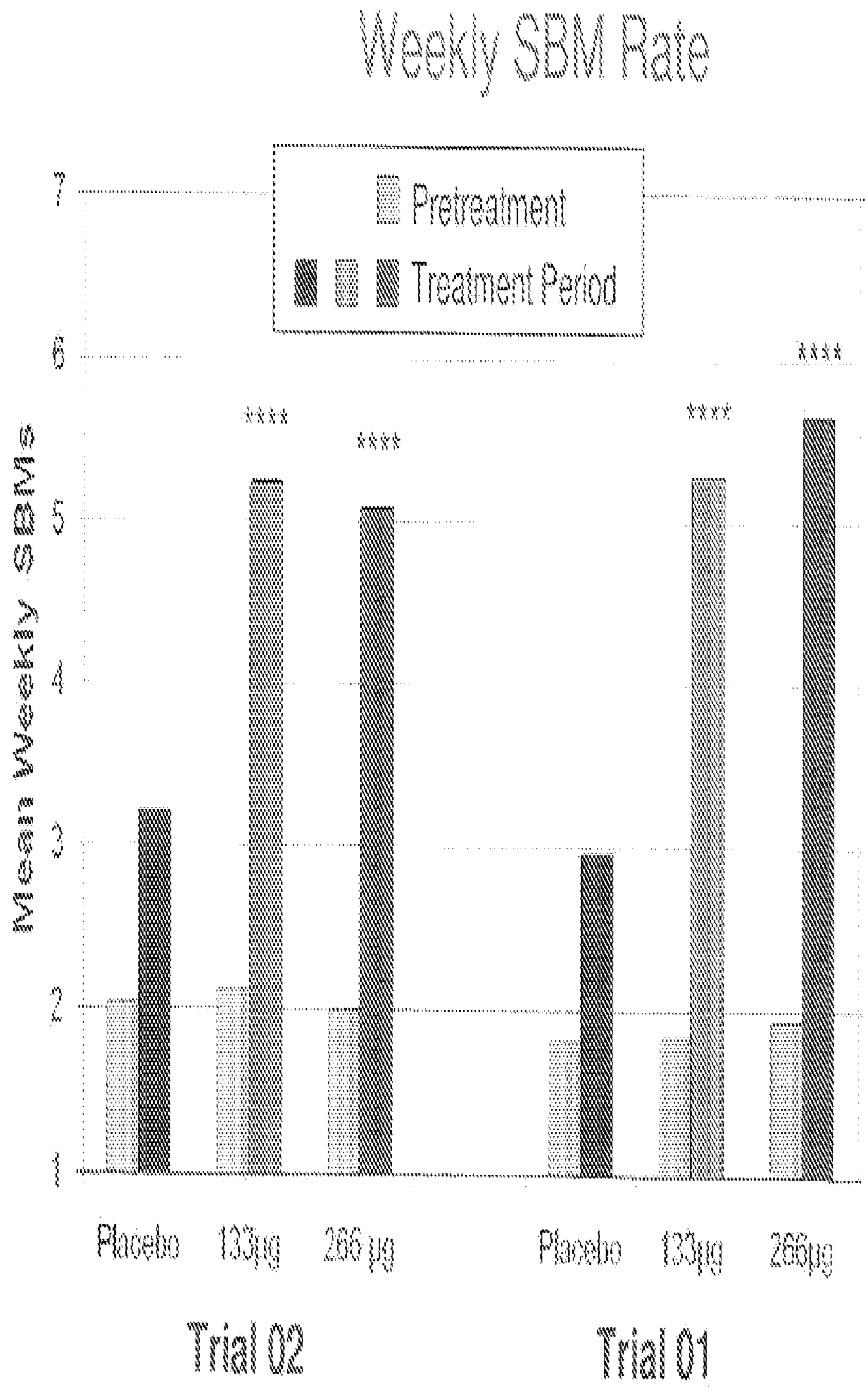
FIGURE 4



REPLACEMENT SHEET
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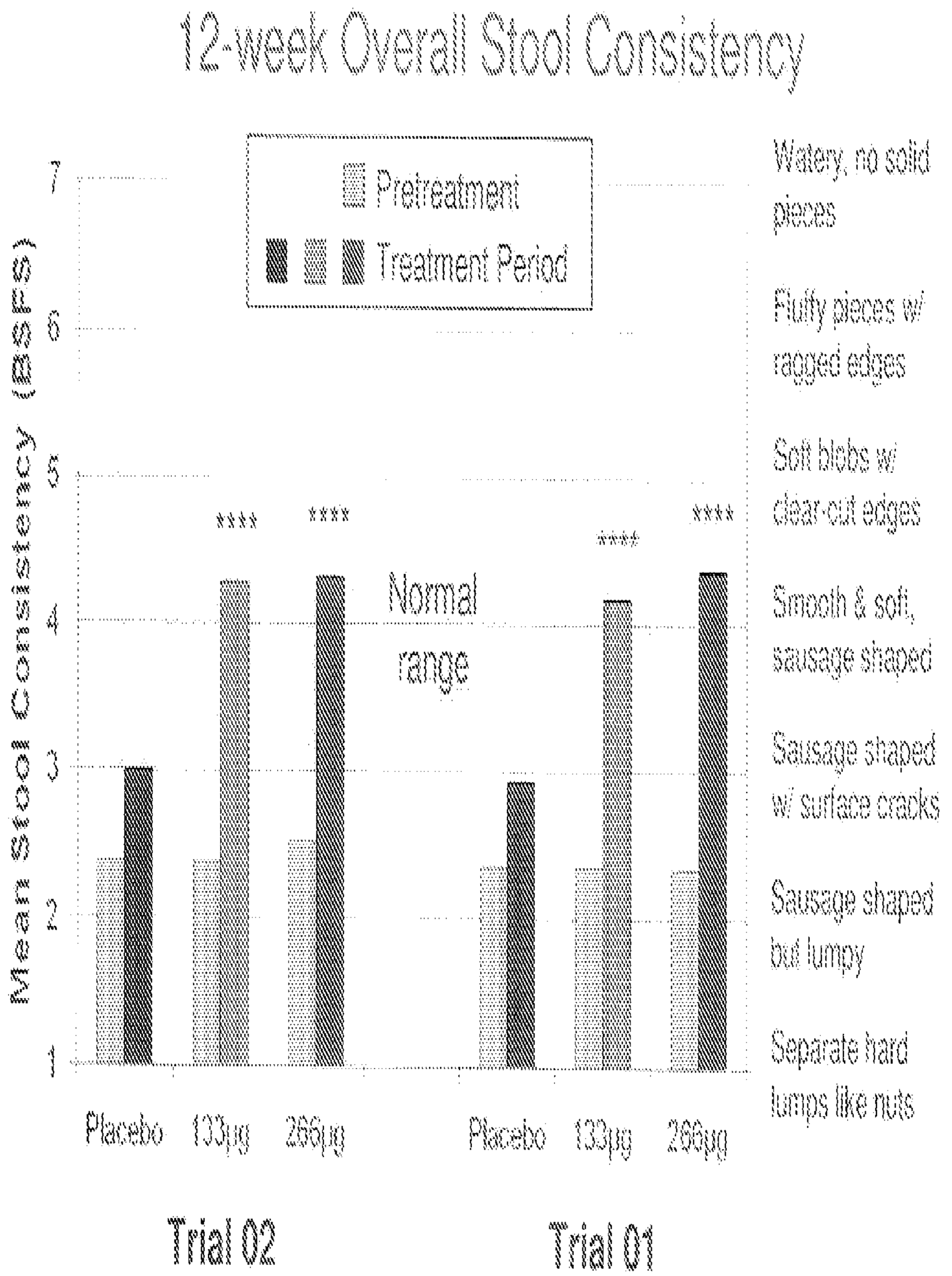
FIGURE 5



*≤ 0.05 **≤ 0.01 ***≤ 0.001 ****≤ 0.0001 (vs. placebo, ANCOVA test)
Note: ITT Populations

REPLACEMENT SHEET
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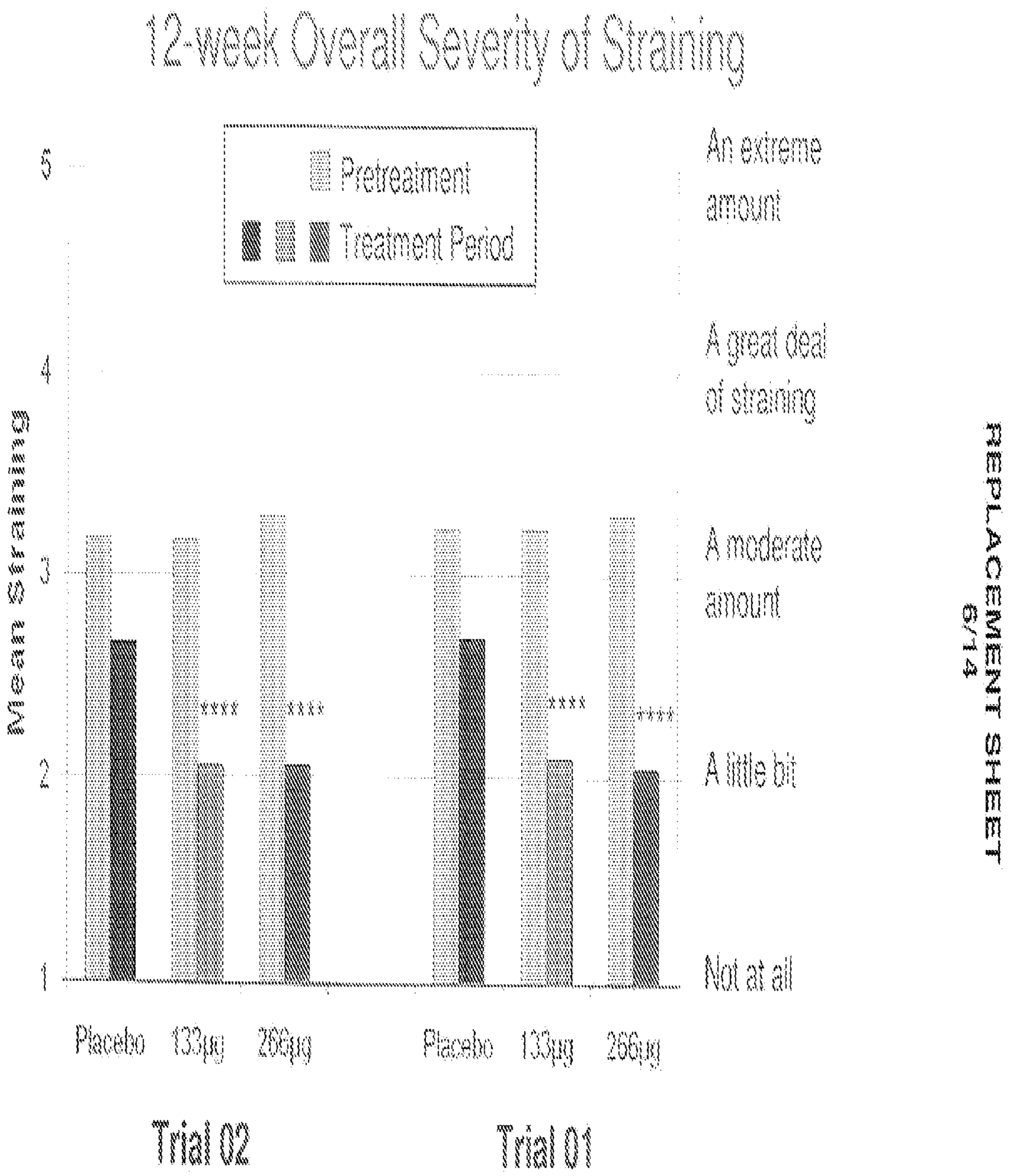
FIGURE 6



*≤ 0.05 **≤ 0.01 ***≤ 0.001 ****≤ 0.0001 (vs. placebo, ANCOVA test)
Note: ITT Populations

REPLACEMENT SHEET
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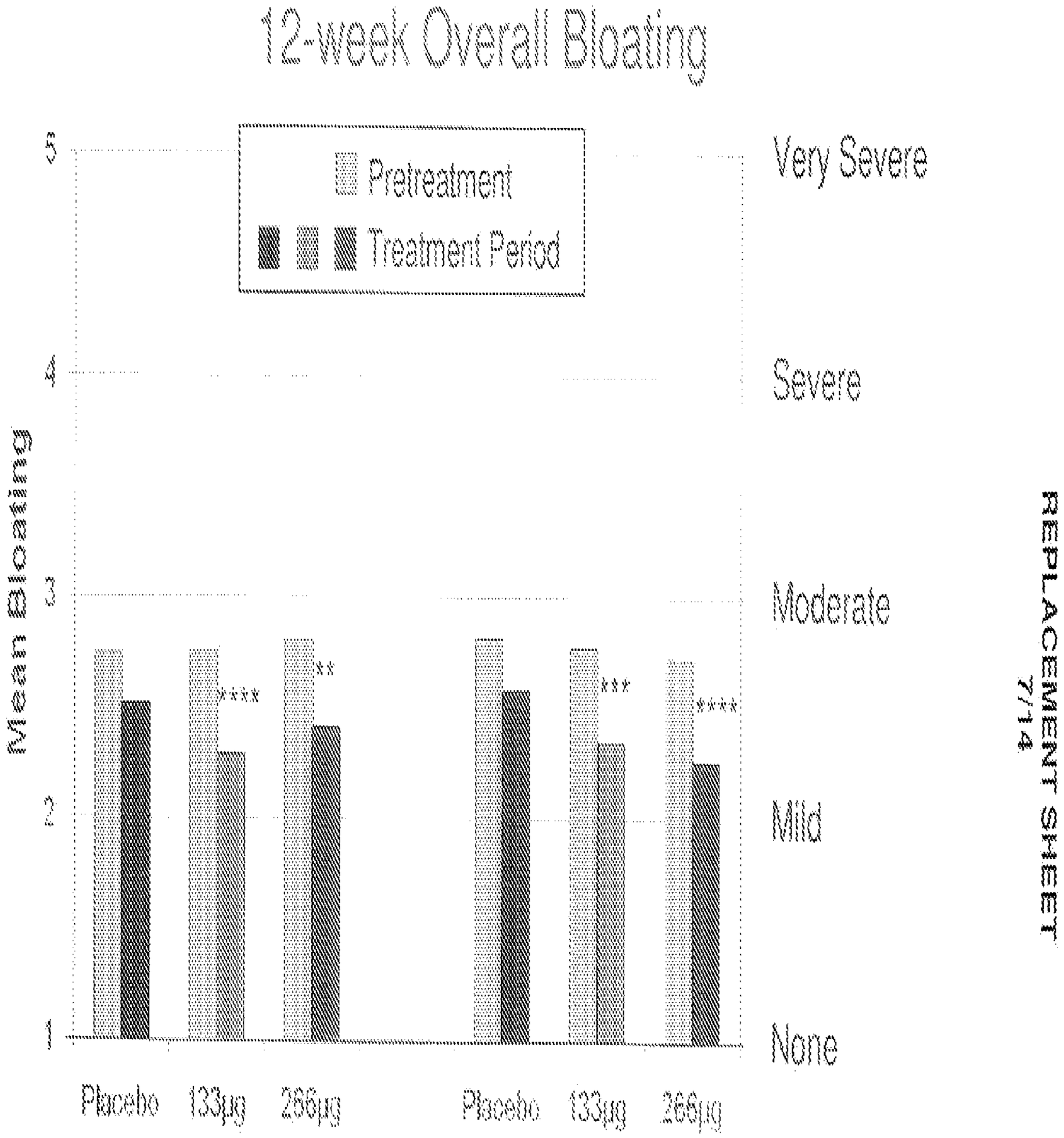
FIGURE 7



REPLACEMENT SHEET
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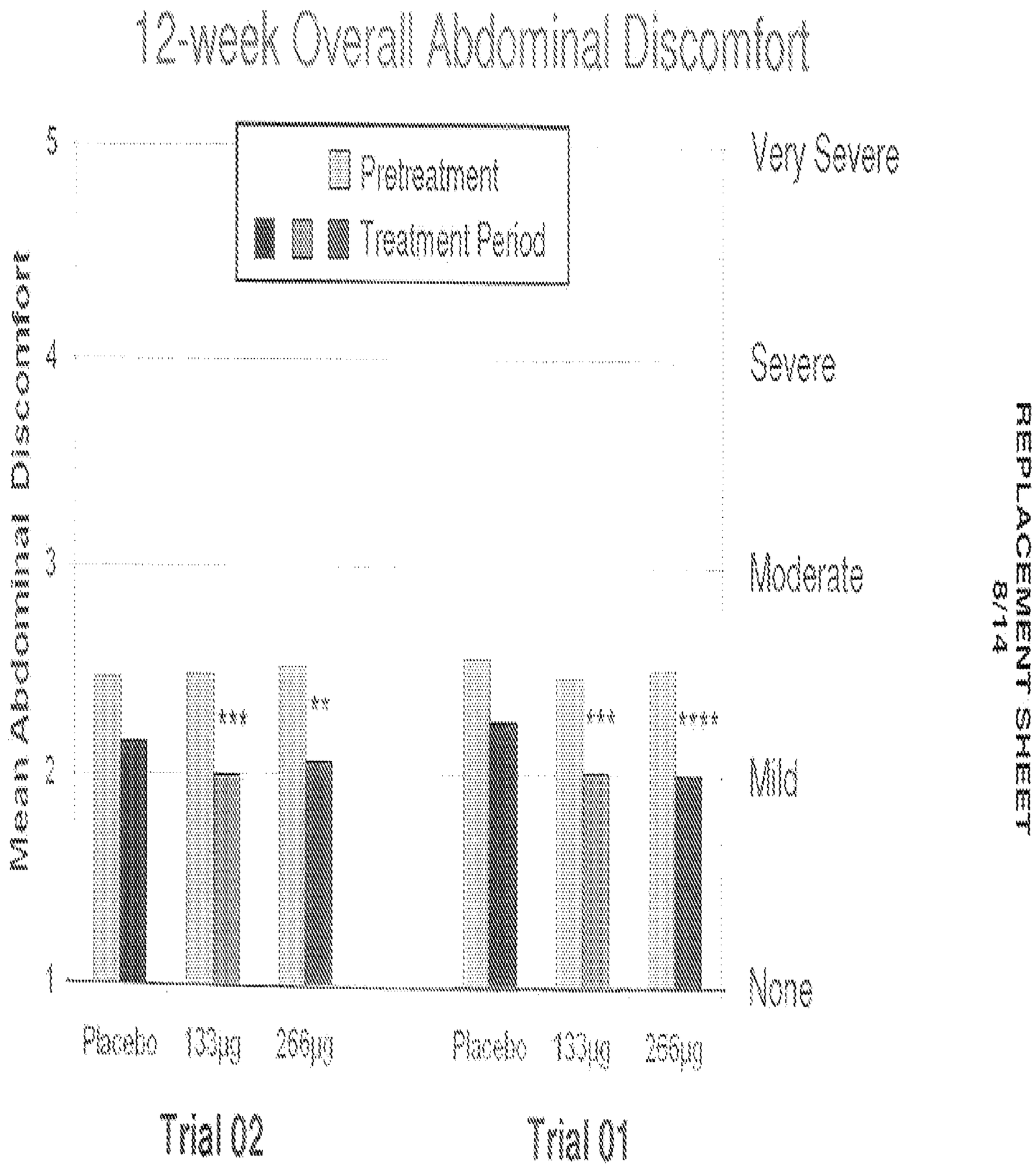
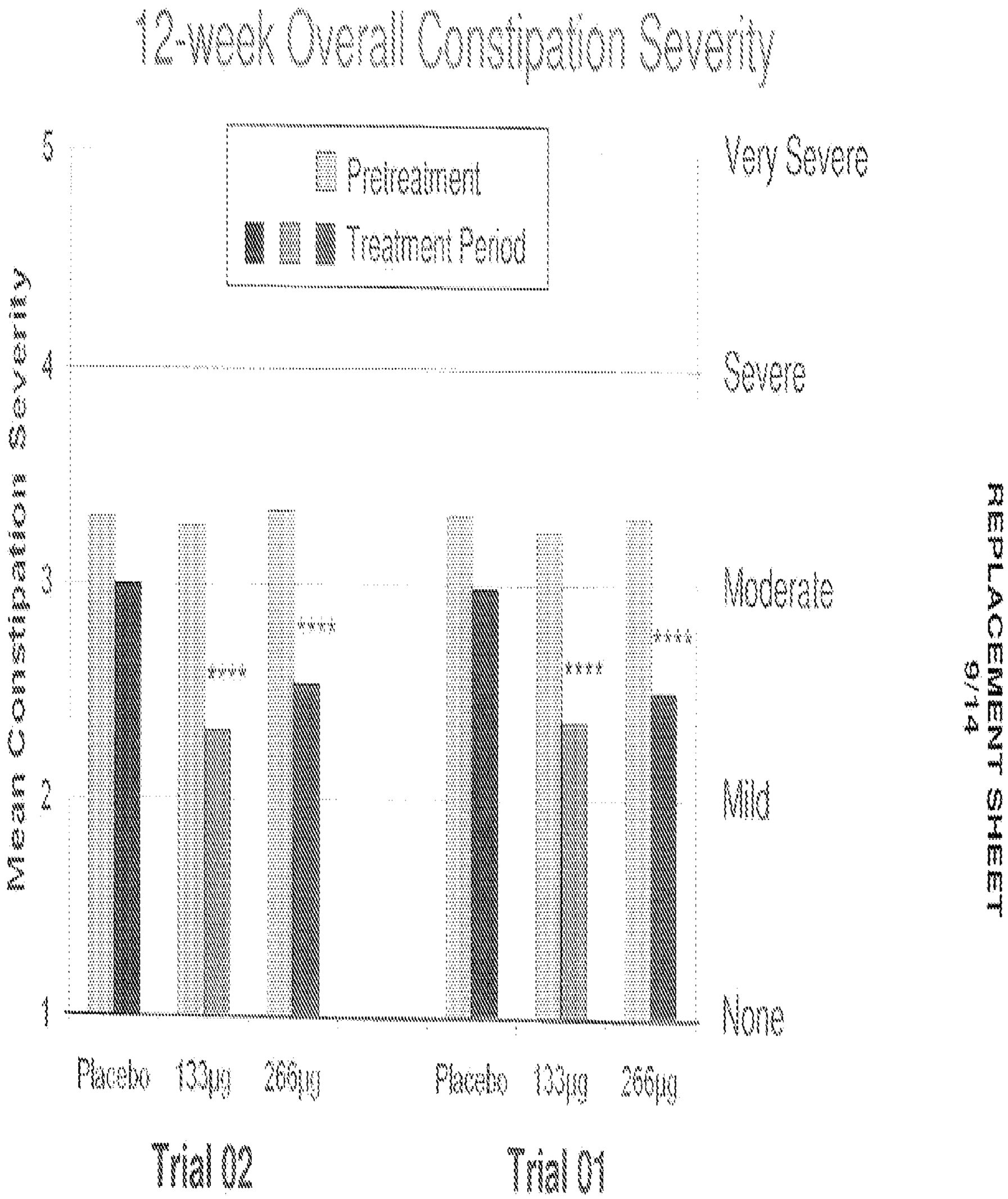
*≤ 0.05 **≤ 0.01 ***≤ 0.001 ****≤ 0.0001 (vs. placebo, ANCOVA test)
Note: ITT Populations

FIGURE 8



*≤ 0.05 **≤ 0.01 ***≤ 0.001 ****≤ 0.0001 (vs. placebo, ANCOVA test)
Note: ITT Populations

FIGURE 9



*≤ 0.05 **≤ 0.01 ***≤ 0.001 ****≤ 0.0001 (vs. placebo, ANCOVA test)
Note: ITT Populations

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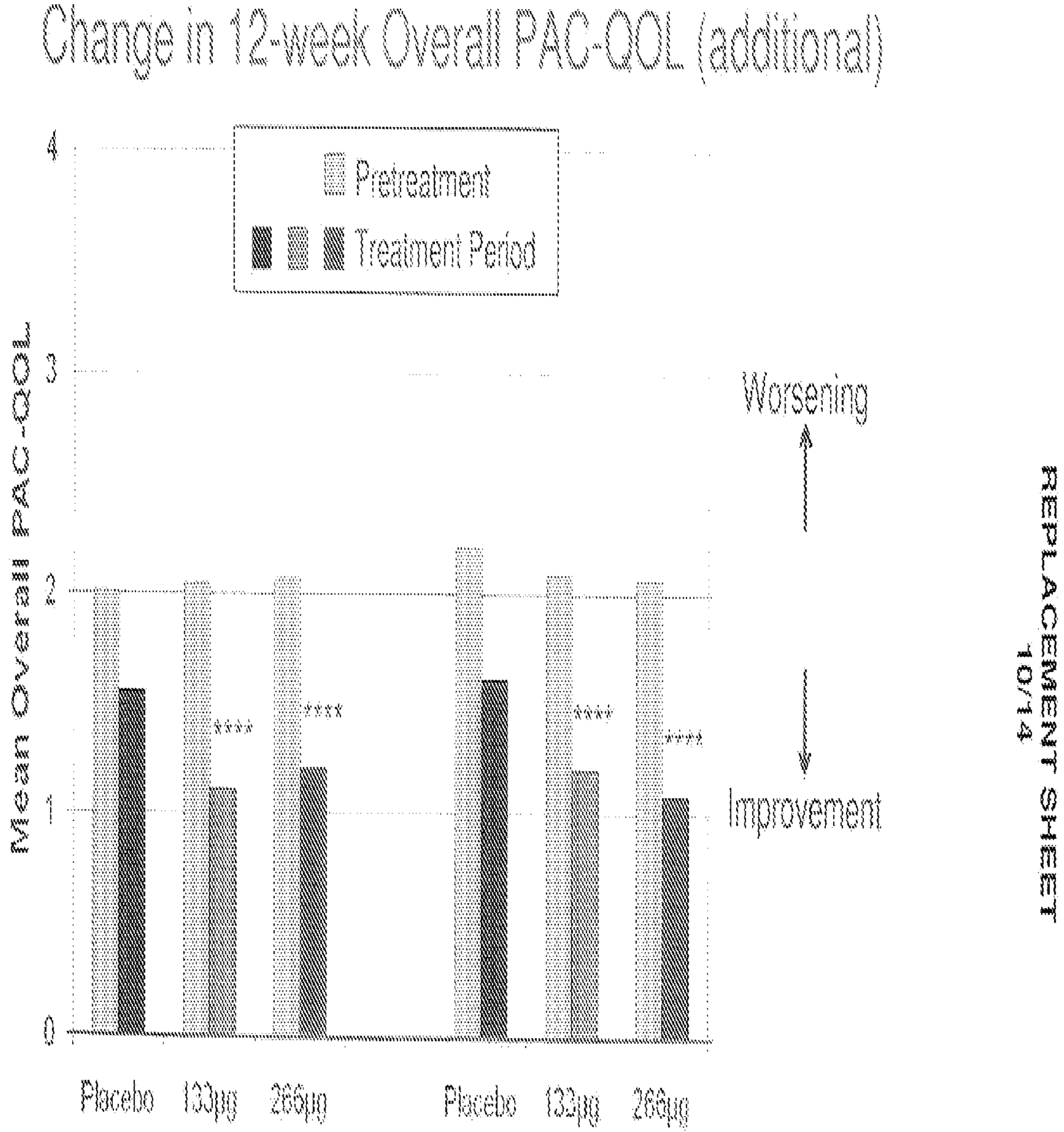
FIGURE 10



*≤ 0.05 **≤ 0.01 ***≤ 0.001 ****≤ 0.0001 (vs. placebo, ANCOVA test)
Note: ITT Populations

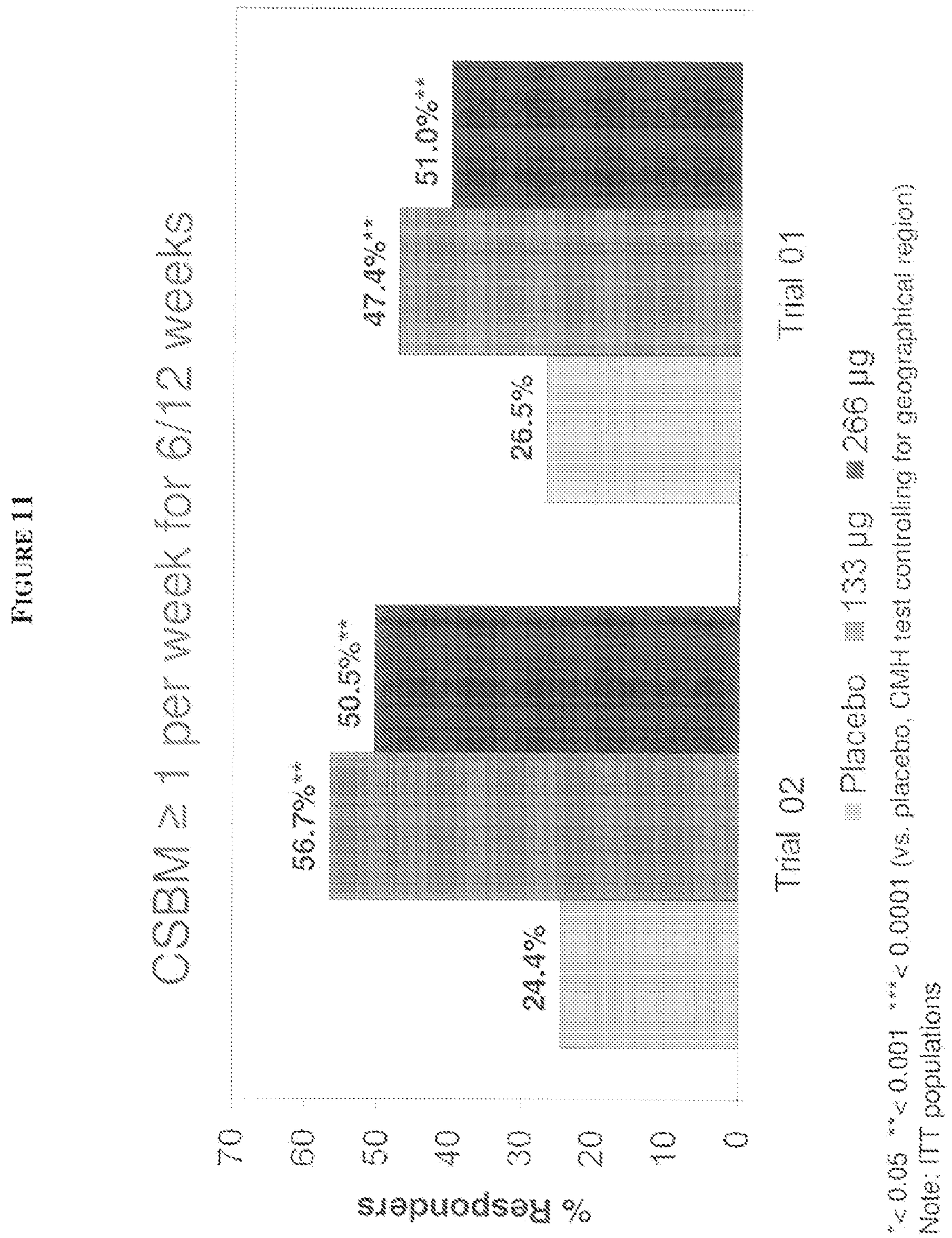

CSBM ≥ 1 per week for 6/12 weeks
% responders
70
60
50
40
30
20
10
0
24.4%
56.7%**
50.5%**
26.5%
47.4%**
51.0%**
Trial 02
Trial 01
Placebo
150 µg
300 µg
*< 0.05 **< 0.001 ***< 0.0001 (vs. placebo, CMH test controlling for geographical region)
Note: ITT populations

FIGURE 11

FIGURE 12A

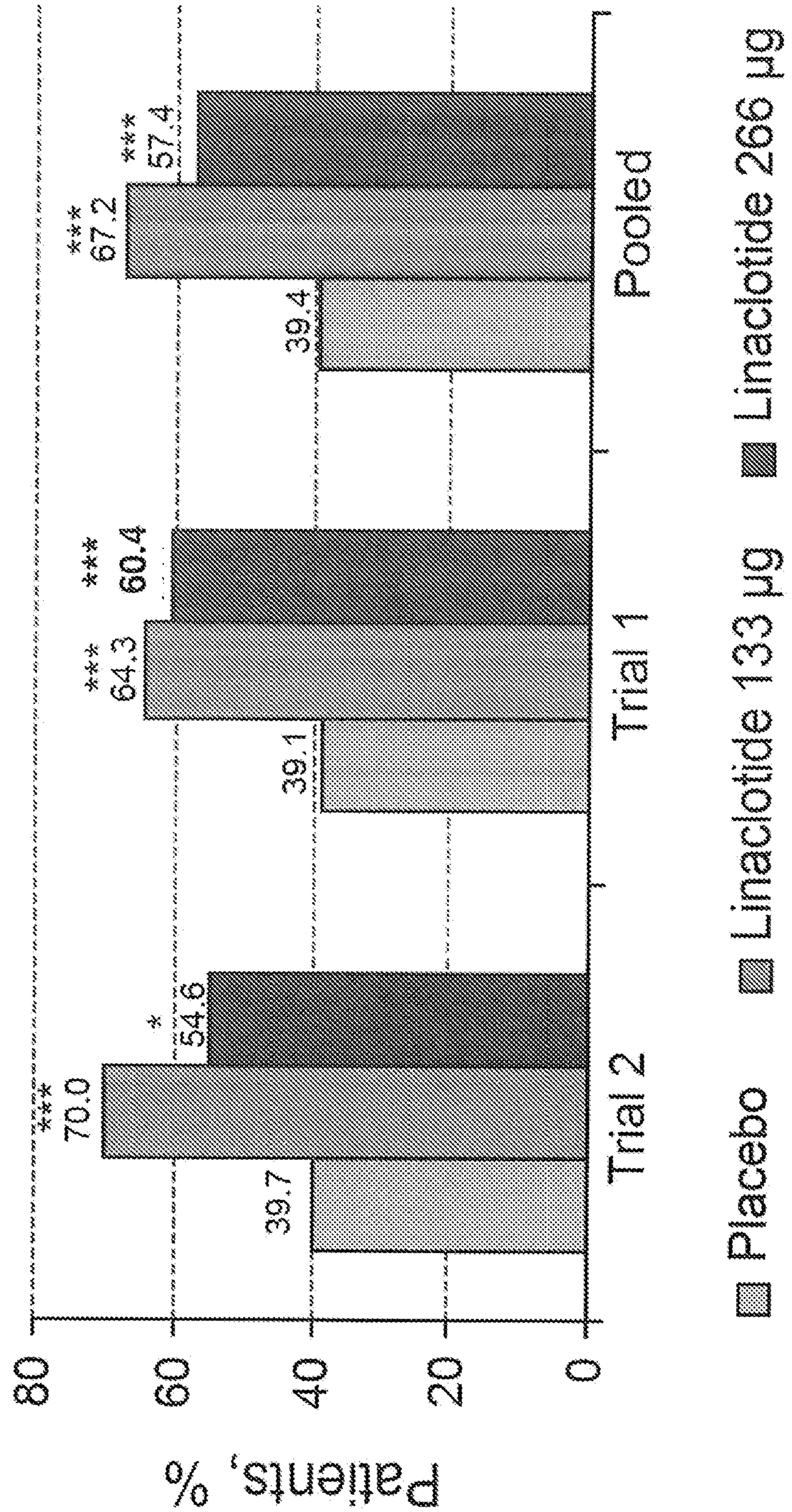

Percent of Patients Reporting SBM Within 24 Hours of Initial Dose
Patients, %
80
60
40
20
0
Trial 1
Trial 2
Pooled
64.3
***
60.4
***
39.7
70.0
***
54.6
*
39.1
67.2
***
57.4
***
39.4
Placebo
Linaclotide 133 µg
Linaclotide 266 µg
** P<0.001, ***P<0.0001 vs placebo

FIGURE 12B

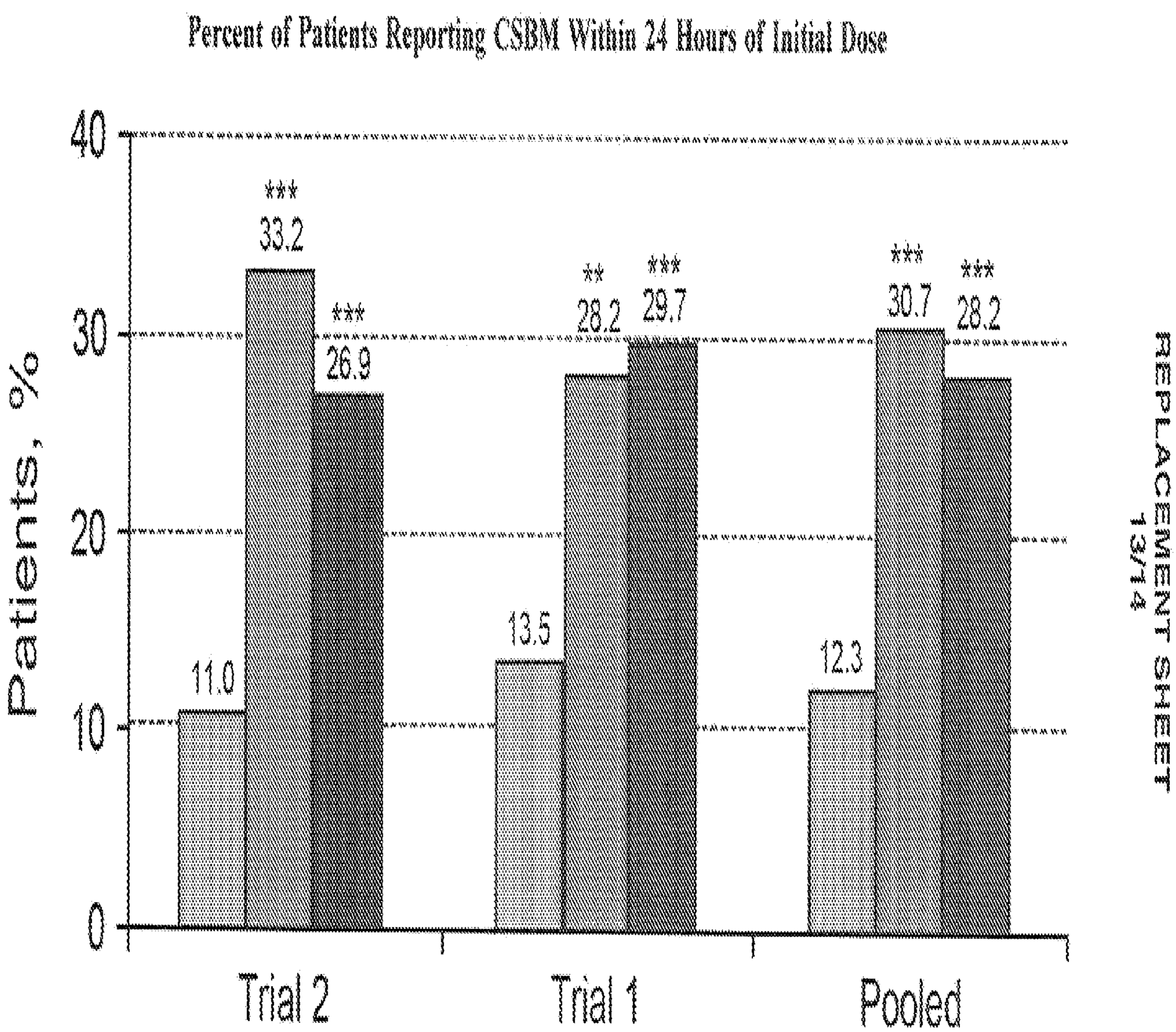
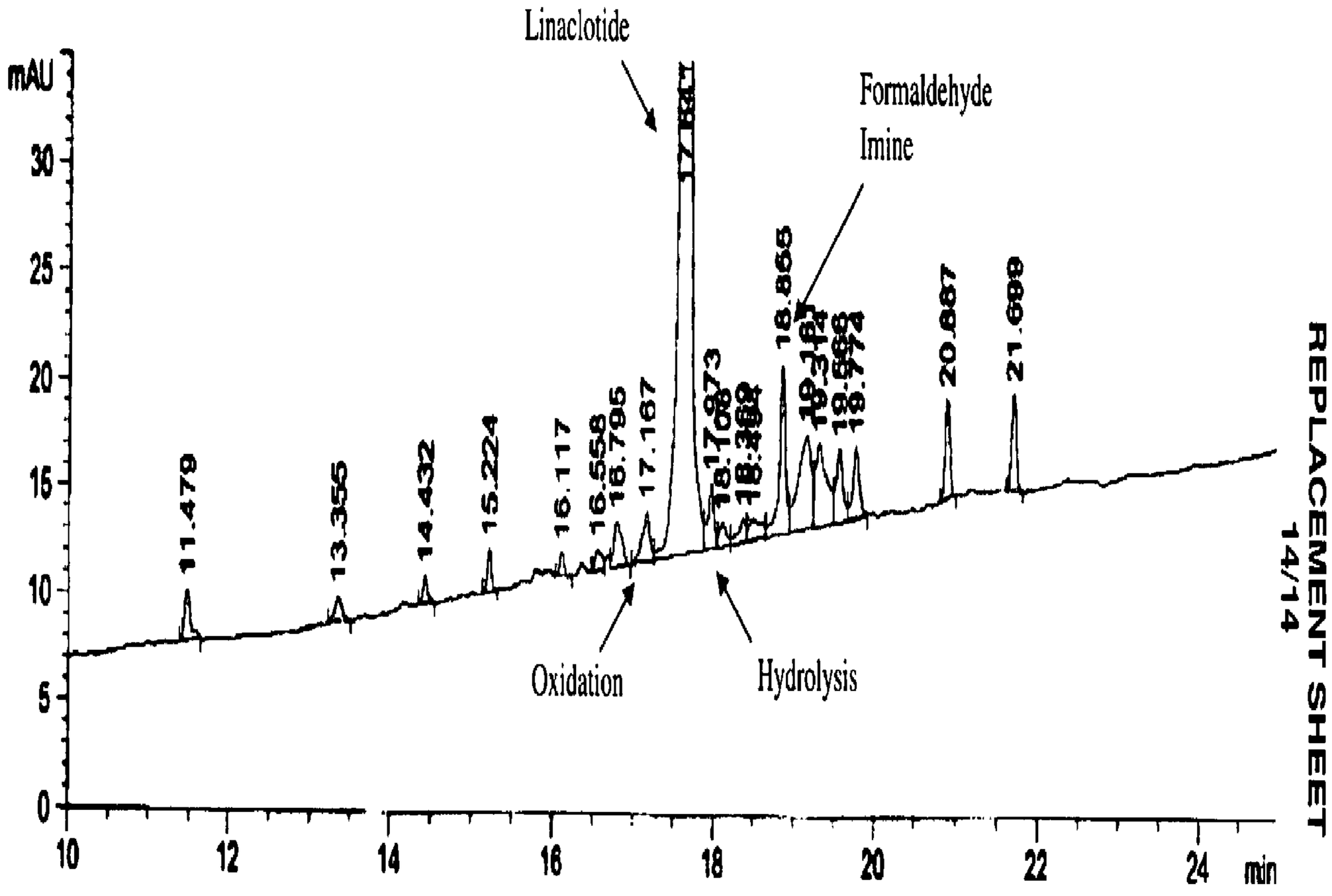


FIGURE 13


Linaclotide
Formaldehyde Imine
Oxidation
Hydrolysis
mAU
30
25
20
15
10
5
0
10
12
14
16
18
20
22
24
min
11.479
13.355
14.432
15.224
16.117
16.558
16.795
17.187
18.866
20.897
21.989
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