PRODUCT MONOGRAPH

PrCONSTELLA®

Linaclotide capsules

72 mcg, 145 mcg and 290 mcg linaclotide

Guanylate Cyclase-C Agonist

Allergan Inc.
85 Enterprise Blvd., Suite 500
Markham, Ontario
L6G 0B5

Date of Preparation:
August 28, 2018

Submission Control No: 218177

CONSTELLA® is a registered trademark of Ironwood Pharmaceuticals, Inc. used under licence by Allergan Inc.

© 2018 Allergan. All Rights Reserved.

Table of Contents

PrCONSTELLA®

Linaclotide capsules
72 mcg, 145 mcg and 290 mcg linaclotide

Guanylate Cyclase-C Agonist

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules 72 mcg, 145 mcg, 290mcg	Gelatin, microcrystalline cellulose For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

INDICATIONS AND CLINICAL USE

Irritable Bowel Syndrome with Constipation (IBS-C)
CONSTELLA® (linaclotide capsules) is indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

Chronic Idiopathic Constipation (CIC)
CONSTELLA® is indicated for the treatment of chronic idiopathic constipation (CIC) in adults.

The efficacy of **CONSTELLA®** for the treatment of IBS-C and CIC has been established in double-blind, placebo-controlled studies of up to 26 and 12 weeks duration, respectively [see CLINICAL TRIALS].

Geriatrics (≥ 65 years of age):
Irritable Bowel Syndrome with Constipation
Of 1,605 IBS-C patients in the placebo-controlled clinical studies of **CONSTELLA®**, 85 (5%) were at least 65 years of age, while 20 (1%) were at least 75 years old. Clinical studies of **CONSTELLA®** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Idiopathic Constipation
Of 2,498 CIC patients in the placebo-controlled clinical studies of **CONSTELLA**®, 273 (11%) were at least 65 years of age, while 56 (2%) were at least 75 years old. Clinical studies of **CONSTELLA**® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Pediatrics (< 18 years of age):
CONSTELLA® is contraindicated in children under 6 years of age and is not recommended for use in children between 6 and 18 years of age as the safety and efficacy of **CONSTELLA**® in pediatric patients have not been established [see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, and TOXICOLOGY, Reproductive and Developmental Toxicity].

CONTRAINDICATIONS

CONSTELLA® (linaclotide capsules) is contraindicated in:

- pediatric patients under 6 years of age [see WARNINGS AND PRECAUTIONS].
- patients who are hypersensitive to linaclotide or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

CONSTELLA® (linaclotide capsules) is contraindicated in children up to 6 years of age and is not recommended in children between 6 and 18 years of age [see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Special Populations, TOXICOLOGY, Reproductive and Developmental Toxicity].

Gastrointestinal

Diarrhea
Diarrhea was the most common adverse reaction of **CONSTELLA**®-treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. The incidence of diarrhea was similar between IBS-C and CIC populations. The incidence of diarrhea was higher in linaclotide-treated patients than placebo-treated patients (see ADVERSE REACTIONS section). Severe diarrhea was reported in 2% of the 145 mcg and 290 mcg **CONSTELLA**®-treated patients, and in <1% of 72 mcg **CONSTELLA**®-treated CIC patients.

Instruct patients to stop **CONSTELLA**® if severe diarrhea occurs and to contact their healthcare provider, who should consider dose suspension [see ADVERSE REACTIONS].

Special Populations

Pregnant Women: There are no adequate and well-controlled studies with **CONSTELLA**® in pregnant women. In animal developmental studies, adverse fetal effects were observed only with maternal toxicity and at doses of linaclotide much higher than the maximum recommended human dose. **CONSTELLA**® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see TOXICOLOGY, Teratology Studies].

Nursing Women: It is not known whether linaclotide is excreted in human milk; however, linaclotide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses [see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics].

Caution should be exercised when **CONSTELLA**® is administered to nursing women.

Pediatrics (< 18 years of age): **CONSTELLA**® is contraindicated in children under 6 years of age and is not recommended for use in children between 6 and 18 years of age as the safety and efficacy of **CONSTELLA**® in pediatric patients have not been established. As guanylate cyclase-C (GC-C) is known to be overexpressed at early ages, children may be particularly sensitive to the effects of **CONSTELLA**® and may be more likely to develop diarrhea and its potentially serious consequences [see CONTRAINDICATIONS, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, and TOXICOLOGY, Reproductive and Developmental Toxicity].

Geriatrics (≥ 65 years of age):
Irritable Bowel Syndrome with Constipation
Of 1,605 IBS-C patients in the placebo-controlled clinical studies of **CONSTELLA**®, 85 (5%) were at least 65 years of age, while 20 (1%) were at least 75 years old. Clinical studies of **CONSTELLA**® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Idiopathic Constipation
Of 2,498 CIC patients in the placebo-controlled clinical studies of **CONSTELLA**®, 273 (11%) were at least 65 years of age, while 56 (2%) were at least 75 years old. Clinical studies of **CONSTELLA**® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of **CONSTELLA**® (linaclotide capsules) in irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) was evaluated in 5,505 patients who were exposed to linaclotide in the Phase 2 and 3 clinical studies. Total exposure of IBS-C patients to linaclotide was 2,253 patient-years and total exposure of CIC patients to linaclotide was 1,636 patient-years.

Oral doses from 72 mcg to 966 mcg once daily were evaluated. Approximately 2,570 patients were treated for 6 months or longer, 2,040 patients for 1 year or longer, and 1,220 patients for 18 months or longer (not mutually exclusive). **CONSTELLA**® was generally well-tolerated, with most adverse events being mild to moderate in intensity.

The most commonly observed adverse reaction in both the **CONSTELLA**®-treated IBS-C and CIC patients in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) was diarrhea.

In placebo-controlled trials in patients with IBS-C, 9.4% of patients treated with 290 mcg of **CONSTELLA**® and 2.9% of patients treated with placebo discontinued prematurely due to adverse reactions. In the **CONSTELLA**® treatment group, the most common reasons for discontinuation due to adverse reactions were diarrhea (5.3%) and abdominal pain (1.2%). In comparison, less than 1% of patients in the placebo group withdrew due to diarrhea or abdominal pain.

In placebo-controlled trials in patients with CIC, 2.9% of patients treated with 72 mcg and 6.3% of patients treated with 145 mcg of **CONSTELLA**® discontinued prematurely due to adverse reactions compared with 2.4% of patients treated with placebo. In the **CONSTELLA**® treatment groups, the most common reasons for discontinuation due to adverse reactions were diarrhea (2.4% with 72 mcg and 3.9% with 145 mcg) and abdominal pain (0 with 72 mcg and 0.7% with 145 mcg). In comparison, 0.2% and 0.4% of patients in the placebo group withdrew due to diarrhea and abdominal pain respectively.

In placebo-controlled trials in patients with IBS-C, a total of 0.7% of patients treated with 290 mcg of **CONSTELLA**® and 1.1% of patients treated with placebo experienced at least 1 serious adverse event. There were no serious adverse events of diarrhea. Of the 7 serious adverse events that were reported in the **CONSTELLA**® patients, 2 (pericarditis and pericardial effusion in 1 patient) were possibly related to treatment. Overall, serious adverse events were low and there was no obvious pattern in the types of serious adverse events experienced in either the placebo or **CONSTELLA**® group.

In placebo-controlled trials in patients with CIC, 0.7% of patients treated with 72 mcg and 1.0% of patients treated with 145 mcg of **CONSTELLA**® experienced at least 1 on-therapy serious adverse event compared with 1.7% of patients treated with placebo. There were no serious adverse events of diarrhea. Of the12 serious adverse events that were reported in the

CONSTELLA® patients, 3(colitis, bronchitis and atrial fibrillation in 1 patient each) were possibly related to treatment. Overall, serious adverse events were low and there was no obvious pattern in the types of serious adverse events experienced in either the placebo or **CONSTELLA**® group.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Irritable Bowel Syndrome with Constipation (IBS-C)

Common Adverse Reactions

The data described below reflect exposure to **CONSTELLA**® in the two double-blind, placebo-controlled clinical trials involving 1,605 adult patients with IBS-C. Patients were randomized to receive placebo or 290 mcg **CONSTELLA**® once daily on an empty stomach, for up to 26 weeks. Demographic characteristics were comparable between the **CONSTELLA**® treatment group and placebo [see CLINICAL TRIALS].

Table 1 provides the incidence of adverse reactions reported in ≥ 1% of **CONSTELLA**®-treated IBS-C patients and at an incidence that was greater than in placebo-treated patients in the Phase 3 placebo-controlled trials.

Table 1: Adverse Reactions Occurring in ≥ 1% of CONSTELLA®-Treated Patients and at an Incidence Greater than in Placebo-Treated Patients in Two Phase 3 Placebo-Controlled Trials in IBS-C

System Organ Class Preferred Term	CONSTELLA® 290 mcg /day n=807 (%)	Placebo n=798 (%)
Gastrointestinal disorders		
Diarrhea	19.8	3.0
Abdominal pain	5.1	3.3
Flatulence	4.3	1.9
Abdominal distension	2.2	1.1
Vomiting	1.7	1.3
Gastroesophageal reflux disease	1.2	0.9
General disorders and administration site conditions		
Fatigue	1.5	1.4
Infectious disease		
Gastroenteritis viral	2.6	1.4

Diarrhea

Diarrhea was the most commonly reported adverse reaction of the **CONSTELLA®** -treated patients in the pooled IBS-C Phase 3 placebo-controlled trials. In these trials, 19.8% of **CONSTELLA®**-treated patients reported diarrhea compared to 3.0% of placebo-treated patients. Severe diarrhea was reported in 2.0% of the **CONSTELLA®**-treated patients versus less than 1% of the placebo-treated patients, and 5.3% of the **CONSTELLA®**-treated patients discontinued due to diarrhea versus less than 1% of placebo-treated patients. The majority of reported cases of diarrhea started within the first 2 weeks of **CONSTELLA®** treatment. [see WARNINGS AND PRECAUTIONS, Gastrointestinal].

Other Adverse Reactions Observed in Clinical Studies

Other adverse reactions that were reported in less than 1% of IBS-C patients are listed below by body system:

Gastrointestinal disorders: Abdominal discomfort, anal fissure, bowel movement irregularity, defecation urgency, eructation, fecal incontinence, feces discoloured, frequent bowel movements, gastrointestinal pain, gastrointestinal sounds abnormal, hemorrhoidal hemorrhage, rectal fissure, rectal tenesmus

Infections and infestations: Gastroenteritis

Investigations: Blood bicarbonate decreased

Chronic Idiopathic Constipation (CIC)

Common Adverse Reactions

The data described below reflect exposure to **CONSTELLA**® in the two double-blind, placebo-controlled clinical trials involving 1,275 adult patients with CIC. Patients were randomized to receive placebo, 145 mcg **CONSTELLA**® or 290 mcg **CONSTELLA**® once daily on an empty stomach, for at least 12 weeks. Of these patients, 430 patients received **CONSTELLA**® at the recommended dose of 145 mcg once daily, while 422 patients were treated with 290 mcg **CONSTELLA**® once daily. Demographic characteristics were comparable between both **CONSTELLA**® treatment groups and placebo [see CLINICAL TRIALS].

Table 2 provides the incidence of adverse reactions reported in ≥ 1% of **CONSTELLA**®-treated CIC patients in the 145 mcg and 290 mcg **CONSTELLA**® treatment groups and at an incidence that was greater than in placebo-treated patients in the Phase 3 placebo-controlled trials.

Table 2: Adverse Reactions Occurring in ≥ 1% of All CONSTELLA®-Treated Patients and at an Incidence Greater than in Placebo-Treated Patients in the Two Phase 3 Placebo-Controlled Trials in CIC

System Organ Class Preferred Term	CONSTELLA® 145 mcg /day n=430 (%)	CONSTELLA® 290 mcg /day n=422 (%)	CONSTELLA® Both Doses n=852 (%)	Placebo n=423 (%)
Gastrointestinal				
Diarrhea	16.0	14.2	15.1	4.7
Flatulence	5.6	5.0	5.3	5.2
Abdominal pain	4.0	4.7	4.3	3.1
Nausea	3.5	4.3	3.9	3.5
Abdominal distension	3.5	3.6	3.5	2.4
Abdominal pain upper	3.0	1.2	2.1	1.7
Dyspepsia	1.9	0.7	1.3	0.7
Infections and infestations				
Gastroenteritis viral	1.9	0.5	1.2	0.5
Nervous system disorders				
Dizziness	0.9	1.4	1.2	0.5

The safety of a 72 mcg dose was evaluated in a placebo-controlled trial in which 1223 patients were randomized to **CONSTELLA**® 72 mcg, 145 mg or placebo once daily for 12 weeks (Trial 5). Demographic characteristics were comparable between both **CONSTELLA**® treatment groups and Placebo [see CLINICAL TRIALS].

Table 3 provides the incidence of adverse reactions reported in ≥ 1% of **CONSTELLA**®-treated CIC patients in the 72 mcg or 145 mcg **CONSTELLA**® treatment groups and at an incidence that was greater than in placebo-treated patients in Trial 5.

Table 3: Adverse Reactions Occurring in ≥ 1% of CONSTELLA®-Treated Patients at Either Dose and at an Incidence Greater than in Placebo-Treated Patients in Trial 5

System Organ Class Preferred Term	CONSTELLA® 72 mcg /day n=411 (%)	CONSTELLA® 145 mcg /day n=411 (%)	Placebo n=401 (%)
Gastrointestinal			
Diarrhea	19.2	22.1	7.0
Abdominal distension	2.2	1.2	0.5
Flatulence	1.5	0.7	1.2
Infections and infestations			
Upper Respiratory Tract Infection	1.5	1.5	1.2
Sinusitis	1.0	1.9	0.2
Nasopharyngitis	0.5	1.5	0.5

Diarrhea

Diarrhea was the most commonly reported adverse reaction of the **CONSTELLA®**-treated patients in the pooled CIC Phase 3 placebo-controlled trials. Severe diarrhea was reported in less than 1% of the 72 mcg **CONSTELLA®**-treated patients (Trial 5) and in 1.6% (Trials 3 and 4) and 2.4% (Trial 5) of 145 mcg **CONSTELLA®**-treated patients versus less than 1% of the placebo-treated patients (Trials 3 and 4; Trial 5. The majority of reported cases of diarrhea started within the first 2 weeks of **CONSTELLA®** treatment. [see WARNINGS AND PRECAUTIONS, Gastrointestinal].

Other Adverse Reactions Observed in Clinical Studies

Other adverse reactions that were reported in less than 1% of CIC patients are listed below by body system:

Gastrointestinal disorders: Abdominal discomfort, anal fissure, anorectal discomfort, defecation urgency, fecal incontinence, feces discoloured, frequent bowel movements, gastroesophageal reflux disease, gastrointestinal pain, gastrointestinal sounds abnormal, hemorrhoids, mucous stools, proctalgia, rectal spasm

General disorders and administration site conditions: Fatigue

Investigations: Blood magnesium decreased, blood potassium decreased, blood pressure decreased

Metabolism and nutrition disorders: Dehydration, hyponatremia

Nervous system disorders: Presyncope, syncope

Renal and urinary disorders: Azotemia

Vascular disorders: Orthostatic hypotension

DRUG INTERACTIONS

Drug-Drug Interactions

No drug-drug interaction studies have been conducted with **CONSTELLA**® (linaclotide). Linaclotide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses; hence, no systemic drug-drug interactions or drug interactions mediated by plasma protein binding of linaclotide or its metabolite are expected [see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics].

Linaclotide does not interact with the cytochrome P450 enzyme system based on the results of *in vitro* studies. In addition, linaclotide is neither a substrate nor an inhibitor of the efflux transporter P-glycoprotein (P-gp).

Drug-Food Interactions

Taking **CONSTELLA**® immediately after a high fat breakfast resulted in looser stools and a higher stool frequency compared with taking it in the fasted state, in healthy subjects; the effect in patients with IBS-C and CIC has not been established. In clinical trials, **CONSTELLA**® was administered on an empty stomach, at least 30 minutes before breakfast [see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics].

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients should be counselled that improvement of bowel symptoms should occur within the first week of **CONSTELLA**® (linaclotide capsules) treatment, but improvement of abdominal symptoms may take longer [see CLINICAL TRIALS]. Physicians should periodically assess the need for continued treatment with **CONSTELLA**®.

Patients on treatment who experience severe diarrhea should stop **CONSTELLA**® and contact their physician [see WARNINGS AND PRECAUTIONS, Gastrointestinal].

Exceeding the daily dose of 145 mcg for the treatment of CIC is not expected to increase efficacy.

Recommended Dose and Dosage Adjustment

Irritable Bowel Syndrome with Constipation

The recommended dose of **CONSTELLA**® is 290 mcg taken orally once daily on an empty stomach, at least 30 minutes prior to the first meal of the day [see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics].

Chronic Idiopathic Constipation

The recommended dose of **CONSTELLA**® is 145 mcg taken orally once daily on an empty stomach, at least 30 minutes prior to the first meal of the day [see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics]. A dose of 72 mcg may be used depending on individual clinical presentation or response to the starting dose.

Special Populations

No dose adjustments are required for patients with hepatic or renal impairment [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Pediatrics (<18 years of age): CONSTELLA® is contraindicated in children under 6 years of age and is not recommended for use in children between 6 and 18 years of age. [see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, and TOXICOLOGY, Reproductive and Developmental Toxicity].

Missed Dose

In the event that a dose is missed, the patient should skip that dose. Do not take two capsules to account for the missed dose. Wait until it is time for the next dose and then take the usual dose on an empty stomach.

Administration

CONSTELLA® capsules should be taken orally once daily on an empty stomach, at least 30 minutes prior to the first meal of the day. The capsules should be swallowed whole and should not be chewed. For adult patients who have difficulty swallowing, the contents of the capsules may be given in applesauce or water. Sprinkling of **CONSTELLA**® beads on other soft foods or in other liquids has not been tested.

For administration in applesauce:

- Place one teaspoonful of applesauce at room temperature into a clean container
- Open the capsule
- Sprinkle entire contents (beads) on applesauce
- Consume the contents immediately. Do not chew the beads. Do not store the applesauce and beads for later use.

For administration in water:

- Pour approximately 30 mL of bottled water at room temperature into a clean cup

- Open the capsule
- Sprinkle entire contents (beads) into the water
- Gently swirl beads and water for at least 20 seconds
- Swallow the mixture of beads and water immediately
- Add another 30 mL of water to any beads remaining in the cup, swirl for 20 seconds and swallow immediately
- Do not store the bead-water mixture for future use

Note: The drug is coated on the surface of the beads and will dissolve off the beads into the water. The beads will remain visible and will not dissolve. Therefore, it is not necessary to consume all of the beads to deliver the complete dose.

For nasogastric or gastric feeding tube administration in water:

- Open the capsule and empty the beads into a clean container with 30 mL of room temperature bottled water
- Mix by gently swirling beads for at least 20 seconds
- Draw up the bead-water mixture into an appropriately sized catheter-tipped syringe and apply rapid and steady pressure (10 mL / 10 seconds) to dispense the syringe contents into the tube
- After administering the bead-water mixture, flush the nasogastric / gastric tube with a minimum of 10 mL of water
- Add another 30 mL of water to the container and repeat the process
- Use the mixture of beads and water immediately. Do not store for future use.

Note: It is not necessary to flush all of the beads through to deliver the complete dose.

The first meal of the day can be consumed 30 minutes after dosing of **CONSTELLA®**.

OVERDOSAGE

There is limited experience with overdose of **CONSTELLA®** (linaclotide capsules). During the clinical development program of **CONSTELLA®**, single doses of 2897 mcg were administered to 22 healthy volunteers; the safety profile in these subjects was consistent with that in the overall **CONSTELLA®**-treated population, with diarrhea being the most commonly reported adverse reaction.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain and discomfort are associated with altered defecation. The disorder has a spectrum ranging from mild to severe and is associated with deterioration in quality of life. The etiology and pathophysiology

are poorly understood and appear to be multifactorial, resulting from a combination of visceral hypersensitivity, alteration in gastrointestinal (GI) motility, and psychosocial factors. Treatment of IBS is aimed at symptomatic relief of abdominal symptoms (i.e., abdominal pain, abdominal discomfort, and bloating), normalization of defecation, and improvement of quality of life.

Chronic idiopathic constipation (CIC) is a functional GI disorder. Patients with CIC report multiple bowel and abdominal symptoms including straining, gas, hard stools, abdominal discomfort, infrequent bowel movements, bloating, a sense of incomplete evacuation, and abdominal pain. Treatment of CIC is aimed at normalizing the frequency and consistency of bowel movements, as well as relieving the abdominal symptoms commonly associated with this condition.

Mechanism of Action

Linaclotide, a synthetic 14-amino acid peptide, is a potent and selective guanylate cyclase-C (GC-C) agonist with visceral analgesic and secretory activities. This first-in-class orally active peptide is structurally related to the guanylin peptide family, which is involved in the regulation of fluid homeostasis and bowel function of the GI tract. Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. Linaclotide has been shown to both accelerate GI transit and reduce intestinal pain. The linaclotide-induced reduction in visceral pain is thought to be mediated by increased extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves.

Pharmacodynamics

Although the pharmacologic effects of **CONSTELLA®** (linaclotide capsules) in humans have not been fully evaluated, **CONSTELLA®** has been shown, in clinical studies, to accelerate colonic transit, soften stools, and increase stool frequency.

Pharmacokinetics

Absorption: CONSTELLA® is minimally absorbed with low systemic availability following oral administration. Concentrations of linaclotide and its active metabolite in plasma were below the limit of quantitation after oral doses of 145 mcg or 290 mcg were administered. Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration (C_{max}) and half-life ($t_{1/2}$) cannot be calculated.

Distribution: Given that linaclotide plasma concentrations following therapeutic oral doses are not measurable, linaclotide is expected to be minimally distributed to tissues.

Metabolism: Linaclotide is metabolized within the gastrointestinal tract to its principal, active metabolite by loss of the terminal tyrosine moiety. Both linaclotide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring

amino acids.

Excretion: Active peptide recovery in the stool samples of fasted and fed subjects following the daily administration of 290 mcg of linaclotide for seven days averaged ~5 % (fasted) and ~ 3 % (fed) and virtually all as the active metabolite.

Food Effect: In a cross-over study, 18 healthy subjects were administered **CONSTELLA**® 290 mcg for 7 days both in the non-fed and fed state. Neither linaclotide nor its active metabolite was detected in the plasma. Taking **CONSTELLA**® immediately after the high fat breakfast resulted in looser stools and a higher stool frequency compared with taking it in the fasted state. In clinical trials, **CONSTELLA**® was administered on an empty stomach, at least 30 minutes before breakfast.

Special Populations and Conditions

Pediatrics (<18 years of age): Clinical studies to determine the impact of age on the clinical pharmacokinetics of linaclotide have not been conducted as linaclotide is rarely detectable in plasma. **CONSTELLA**® is contraindicated in children under 6 years of age and is not recommended for use in children between 6 and 18 years of age as the safety and efficacy of **CONSTELLA**® in pediatric patients have not been established [see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and TOXICOLOGY, Reproductive and Developmental Toxicity].

Geriatrics: Clinical studies to determine the impact of age on the pharmacokinetics of **CONSTELLA**® have not been conducted. See [WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics] for information regarding patients aged 65 years and older.

Gender: Clinical studies to determine the impact of gender on the pharmacokinetics of **CONSTELLA**® have not been conducted. Gender is not expected to affect the pharmacokinetics of **CONSTELLA**®.

Hepatic Impairment: CONSTELLA® has not been specifically studied in patients who have hepatic impairment. Hepatic impairment is not expected to affect the metabolism or clearance of the parent drug or its metabolite because linaclotide has low systemic availability following oral administration and is metabolized within the gastrointestinal tract.

Renal Impairment: CONSTELLA® has not been specifically studied in patients who have renal impairment. Renal impairment is not expected to affect clearance of the parent drug or its metabolite because linaclotide has low systemic availability following oral administration and is metabolized within the gastrointestinal tract.

STORAGE AND STABILITY

Store at room temperature (15°C to 25°C).

Keep **CONSTELLA**® (linaclotide capsules) in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles tightly closed in a dry place.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CONSTELLA® (linaclotide capsules) contains linaclotide-coated beads in hard gelatin capsules. **CONSTELLA**® is available as 72 mcg, 145 mcg or 290 mcg capsules for oral administration.

72 mcg Capsules: Each 72 mcg white to off-white, opaque, hard, gelatin capsule is imprinted with grey imprint "FL 72". Available in bottles of 4 or 30 capsules.

145 mcg Capsules: Each 145 mcg white to off-white, opaque, hard, gelatin capsule is imprinted with a grey imprint "FL 145." Available in bottles of 4 or 30 capsules.

290 mcg Capsules: Each 290 mcg white to off-white, opaque, hard, gelatin capsule is imprinted with a grey imprint "FL 290." Available in bottles of 4 or 30 capsules.

Composition:
The inactive ingredients for the 145 mcg and 290 mcg **CONSTELLA**® capsules include: calcium chloride dihydrate, gelatin, hypromellose, iron oxide black, iron oxide yellow, L-leucine, microcrystalline cellulose, shellac glaze, and titanium dioxide.

The inactive ingredients for the 72 mcg **CONSTELLA**® capsules include: calcium chloride dihydrate, gelatin, L-histidine, iron oxide black, iron oxide yellow, microcrystalline cellulose, polyvinyl alcohol, shellac glaze, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

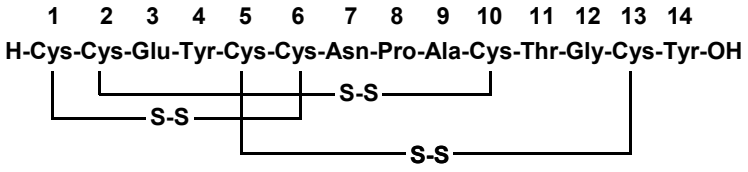
Proper name: Linaclotide

Chemical name: L-cysteinyl-L-cysteinyl-L-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonyl-glycyl-L-cysteinyl-L-tyrosine, cyclic (1-6), (2-10), (5-13)-tris (disulfide)

Molecular formula: $C_{59}H_{79}N_{15}O_{21}S_6$

Molecular weight: 1526.8

Structural formula: Linaclotide is a 14-amino acid peptide with the following sequence:



Physicochemical properties: Linaclotide is an amorphous, white to off-white powder. It is slightly soluble in water and aqueous sodium chloride (0.9%).

CLINICAL TRIALS

Irritable Bowel Syndrome with Constipation (IBS-C)

Study Demographics and Trial Design

The efficacy of **CONSTELLA®** (linaclotide capsules) for the treatment of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients (Trials 1 and 2). A total of 800 patients in Trial 1 and 804 patients in Trial 2 received treatment with **CONSTELLA®** 290 mcg or placebo once daily, and were evaluated for efficacy. A summary of trial designs and patient demographics is presented in Table 4 below. In the two pivotal trials, 77% of patients were White, 19% were Black, and 12% were Hispanic.

Table 4: Summary of Patient Demographics for Clinical Trials Supporting Efficacy of CONSTELLA® in the Treatment of IBS-C (Intention-to-Treat [ITT] Population)

Trial #	Trial Design/Duration	Oral Dosage	Study Subjects (N) [Female/Male (F/M)]	Mean Age (Range)	Mean Baseline Characteristics
1	12-week, randomized, multicenter, double-blind, placebo-controlled, Plus 4-week randomized withdrawal (RW) period	**CONSTELLA®** 290 mcg, once daily	N=800 [F=724; M=76]	43.5 (18-84)	CSBMs/week: 0.2 (0.0-2.9) Abdominal pain[a] (min, max): 5.6 (2.8-10)
2	26-week, randomized, multicenter, double-blind, placebo-controlled	**CONSTELLA®** 290 mcg, once daily	N=804 [F=720; M=84]	44.3 (18-87)	CSBMs/week: 0.2 (0.0-2.9) Abdominal pain[a] (min, max): 5.6 (2.9-10)

[a] Abdominal pain score based on 11-point numerical rating scale (NRS) (0=none, 10=very severe)
CSBM=Complete Spontaneous Bowel Movement

All patients met Rome II criteria for IBS and were required, during the 2-week baseline period, to meet the following criteria:

- a mean abdominal pain score of at least 3 on a 0-to10-point numeric rating scale
- less than 3 complete spontaneous bowel movements (CSBMs) per week [a CSBM is a spontaneous bowel movement (SBM) that is associated with a sense of complete evacuation; a SBM is a bowel movement occurring in the absence of laxative use], and
- less than or equal to 5 SBMs per week.

The trial designs were identical through the first 12 weeks, and thereafter differed only in that Trial 1 included a 4-week randomized withdrawal (RW) period, and Trial 2 continued for 14 additional weeks (total of 26 weeks) of double-blind treatment. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take bismuth, prokinetic agents, or other drugs to treat IBS-C including laxatives (except for bisacodyl, the protocol-specified rescue medication).

Study Results

Efficacy of **CONSTELLA**® was assessed using overall responder analyses (primary endpoints) and change-from-baseline analyses (secondary endpoints). Results for endpoints were based on information provided daily by patients in electronic diaries, via an interactive voice response system.

Primary Endpoints

The 4 primary efficacy responder endpoints were based on a patient being a weekly responder for either at least 9 out of the first 12 weeks of treatment or at least 6 out of the first 12 weeks of treatment. For the 9 out of 12 weeks combined primary responder endpoint, a patient had to have at least a 30% reduction from baseline in mean abdominal pain, at least 3 CSBMs and an increase of at least 1 CSBM from baseline, all in the same week, for at least 9 out of the first 12 weeks of treatment. Each of the 2 components of the 9 out of 12 weeks combined responder endpoint, abdominal pain and CSBMs, was also a primary endpoint.

For the 6 out of 12 weeks combined primary responder endpoint, a patient had to have at least a 30% reduction from baseline in mean abdominal pain and an increase of at least 1 CSBM from baseline, all in the same week, for at least 6 out of the first 12 weeks of treatment. To be considered a responder for this analysis, patients did not have to have at least 3 CSBMs per week.

In the two pivotal trials (Trials 1 and 2) **CONSTELLA**® demonstrated statistically superior benefits, for the primary endpoint, compared to placebo in the treatment of IBS-C. In both trials, the proportion of patients who were responders to **CONSTELLA**® 290 mcg was statistically significantly higher than with placebo. The primary efficacy results are shown in Table 5 below.

Table 5: Primary Efficacy of CONSTELLA® in IBS-C (ITT Population)

Primary Responder Endpoints	Trial 1			Trial 2		
	CONSTELLA® 290 mcg (N=405)	Placebo (N=395)	Treatment Difference [95% CI]	CONSTELLA® 290 mcg (N=401)	Placebo (N=403)	Treatment Difference [95% CI]
9/12 Week Combined Responder (Abdominal Pain and CSBM Responder)	12.1%[b]	5.1%	7.0% [3.2%, 10.9%]	12.7[c]	3.0%	9.7% [6.1%, 13.4%]
CSBM Responder (≥ 3 CSBMs and Increase ≥ 1 CSBM from Baseline)	19.5[c]	6.3%	13.2% [8.6%, 17.7%]	18.0[c]	5.0%	13.0% [8.7%, 17.3%]
Abdominal Pain Responder (≥ 30% Reduction)	34.3%[a]	27.1%	7.2% [0.9%, 13.6%]	38.9%[c]	19.6%	19.3% [13.2%, 25.4%]
6/12 Week Combined Responder (Abdominal Pain and CSBM Responder)	33.6%[c]	21.0%	12.6% [6.5%, 18.7%]	33.7%[c]	13.9%	19.8% [14.0%, 25.5%]

[a] $p \leq 0.05$, [b] $p < 0.001$, [c] $p < 0.0001$
Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2
CI = Confidence Interval, CSBM=Complete Spontaneous Bowel Movement

Secondary Endpoints

The secondary efficacy endpoints consisted of both responder and change from baseline assessments. The responder endpoints were based on a patient being a CSBM weekly responder or an abdominal pain responder for at least 6 out of the first 12 weeks of treatment. For the 6 out of 12 weeks CSBM responder endpoint, a patient had to have an increase of at least 1 CSBM from baseline for at least 6 out of the first 12 weeks of treatment. For the abdominal pain responder, a patient had to have at least a 30% reduction from baseline in mean abdominal pain.

The change from baseline secondary endpoints were the change from baseline in 12-week CSBM and SBM frequency rate, stool consistency, severity of straining, abdominal pain at its worst, abdominal discomfort, bloating and percent of abdominal pain-free days.

In Trial 1 and 2, for the 6/12 week CSBM and abdominal pain endpoints, statistically significantly more patients receiving **CONSTELLA®** 290 mcg were responders versus placebo (Table 6).

Table 6: Secondary Efficacy of CONSTELLA® in IBS-C (6/12 Week Responder Endpoints, ITT Population)

Secondary Responder Endpoints	Trial 1			Trial 2		
	CONSTELLA® 290 mcg (N=405)	Placebo (N=395)	Treatment Difference (%) [95% CI]	CONSTELLA® 290 mcg (N=401)	Placebo (N=403)	Treatment Difference (%) [95% CI]
CSBM Responder (Increase ≥ 1 CSBM from Baseline)	48.6%[c]	29.6%	19.0% [12.4%, 25.7%]	47.6%[c]	22.6%	25.1% [18.7%, 31.4%]
Abdominal Pain Responder (≥ 30% Abdominal Pain Reduction)	50.1%[b]	37.5%	12.7% [5.8%, 19.5%]	48.9%[c]	34.5%	14.4% [7.6%, 21.1%]

[a] $p \leq 0.05$, [b] $p < 0.001$, [c] $p < 0.0001$
Note: Analyses based on first 12 weeks of treatment for Both Trials 1 and 2
CI=Confidence Interval, CSBM=Complete Spontaneous Bowel Movement

For change-from-baseline endpoints, patients who received **CONSTELLA®** 290 mcg across the 2 trials demonstrated statistically significantly greater improvements compared with patients receiving placebo in both abdominal symptoms (pain, discomfort and bloating) and bowel symptoms (straining, stool frequency and consistency) (Table 7). In a pooled analysis of Trials 1 and 2, 67% of **CONSTELLA®** -treated patients had an SBM within 24 hours of taking their first dose versus 42% of placebo patients ($p < 0.0001$).

Table 7: Secondary Efficacy of CONSTELLA® in IBS-C (Mean Change from Baseline, ITT Population)

	Trial 1			Trial 2		
12-week Parameter	**CONSTELLA® 290 mcg (N=405)**	**Placebo (N=395)**	**LSMD [95% CI]**	**CONSTELLA® 290 mcg (N=401)**	**Placebo (N=403)**	**LSMD [95% CI]**
CSBMs/Week	2.3[c]	0.7	1.6 (1.2, 1.9)	2.2[c]	0.7	1.5 (1.2, 1.9)
SBMs/Week	3.9[c]	1.1	2.8 (2.3, 3.2)	4.0[c]	1.3	2.7 (2.3, 3.2)
Stool Consistency (BSFS Score)	2.1[c]	0.7	1.4 (1.3, 1.6)	1.9[c]	0.6	1.3 (1.1, 1.5)
Straining (5-point Ordinal scale)	-1.3%[c]	-0.7	-0.7 (-0.8, -0.5)	-1.2[c]	-0.7	-0.6 (-0.7, -0.5)
Abdominal Pain at its Worst (11-point NRS)	-1.9[c]	-1.1	-0.7 (-1.0, -0.5)	-1.9[c]	-1.1	-0.8 (-1.0, -0.5)
Abdominal Discomfort (11-point NRS)	-2.0[c]	-1.2	-0.7 (-1.0, -0.5)	-1.9[c]	-1.1	-0.8 (-1.1, -0.6)
Bloating (11-point NRS)	-1.9[c]	-1.1	-0.8 (-1.1, -0.6)	-1.9[c]	-1.0	-0.9 (-1.1, -0.6)
Percent of Abdominal Pain-free Days	9.8[a]	5.3	4.5 (1.9, 7.2)	10.5[b]	4.8	5.7 (2.9, 8.5)

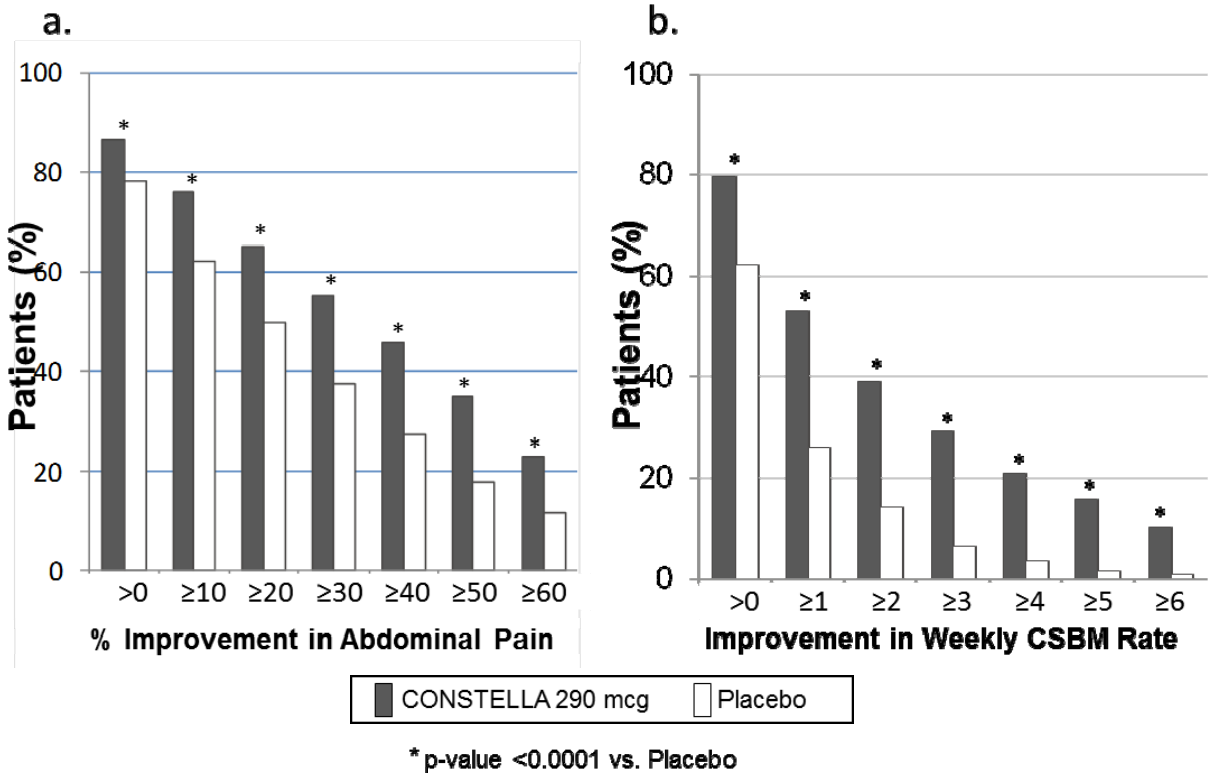
[a] $p \leq 0.05$, [b] $p < 0.001$, [c] $p < 0.0001$
Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2
BSFS=Bristol Stool Form Scale, CI=Confidence Interval, CSBM=Complete Spontaneous Bowel Movement, LSMD=Least Squares Mean Difference, SBM=Spontaneous Bowel Movement, NRS=Numerical Rating Scale

In each trial, improvement from baseline in abdominal pain and CSBM frequency was seen over the first 12-weeks of the treatment periods. For change from baseline in the 11-point abdominal pain scale, **CONSTELLA®** 290 mcg began to separate from placebo in the first week. Maximum effects were seen at Weeks 6 - 9 and were maintained until the end of the study. The mean treatment difference from placebo at Week 12 was a decrease in pain score of approximately 1.0 point in both trials (using an 11-point scale).

The maximum effect on CSBM frequency occurred within the first week. For the change from baseline in CSBM frequency at Week 12, the difference between placebo and **CONSTELLA®** was approximately 1.5 CSBMs per week in both trials.

The proportions of patients who met response criteria of increasing levels of symptom improvement compared to baseline over 12 weeks of treatment were analyzed for both abdominal pain and CSBMs. At each level, a statistically significantly greater proportion of patients treated with **CONSTELLA®** 290 mcg met the response criterion compared to placebo patients (Figure 1).

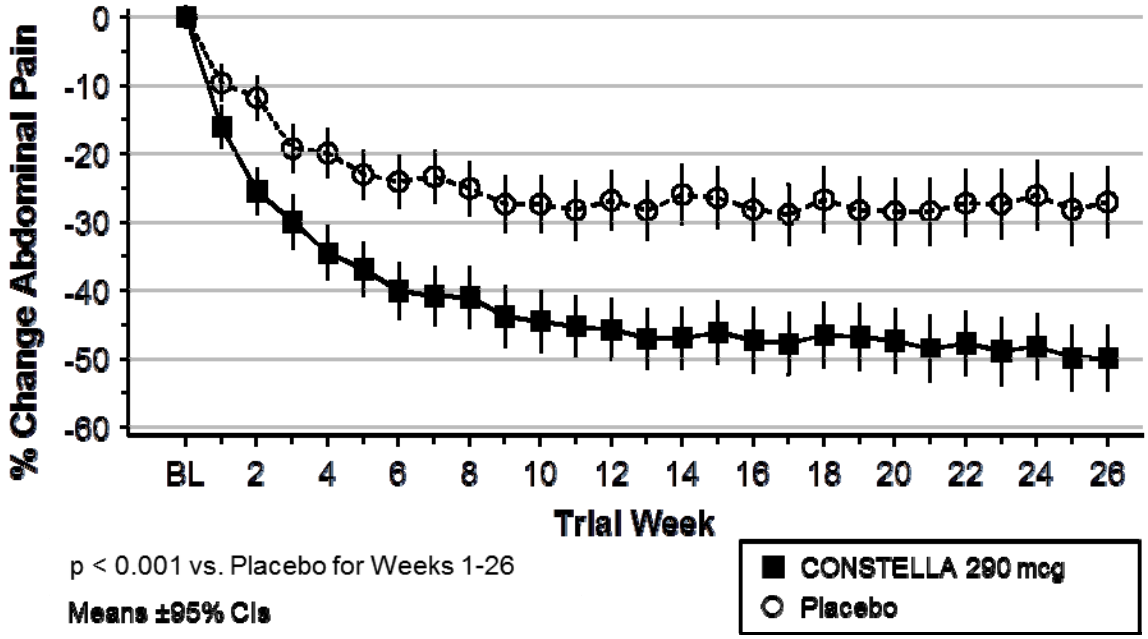
Figure 1: Percentage of Patients with Specified Improvements in (a) Abdominal Pain and (b) CSBMs over the First 12 Weeks of Treatment in IBS-C (Trials 1 & 2, Pooled ITT Population)



CSBM=Complete Spontaneous Bowel Movement

Figure 2 presents results for improvement in abdominal pain (% change from baseline) for each of the 26 weeks of treatment in Trial 2. **CONSTELLA**® 290 mcg demonstrated a statistically significant separation from placebo that was present at the first week and sustained across the 26 weeks of the treatment period ($p < 0.001$ at all time-points during the treatment period). Similar results for improvement in CSBM frequency were demonstrated throughout the 26-week treatment period. Maximum effect on CSBM frequency occurred by Week 1, but the effect on abdominal pain continued to increase over the first 6 to 8 weeks.

Figure 2: Trial 2 - Mean Percentage Improvement in Abdominal Pain by Week over 26 Weeks in IBS-C



CI=Confidence Interval

During the 4-week randomized withdrawal period in Trial 1, patients who received **CONSTELLA**® during the 12-week treatment period were re-randomized to receive placebo or continue treatment on **CONSTELLA**® 290 mcg. In **CONSTELLA**®-treated patients re-randomized to placebo, CSBM frequency and abdominal-pain severity returned toward baseline within 1 week with no evidence of rebound worsening compared to baseline. Patients who continued on **CONSTELLA**® maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to **CONSTELLA**® had an increase in CSBM frequency and abdominal pain levels that were similar to the levels observed in patients taking **CONSTELLA**® during the treatment period.

Quality of Life Assessment

The Irritable Bowel Syndrome-Quality of Life (IBS-QOL) instrument was utilized in the Phase 3 pivotal trials to assess the impact of IBS on a patient's quality of life. The IBS-QOL evaluated 8 dimensions: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships on a 0 to 100 point scale. A pooled analysis of the IBS-QOL data at Week 12 demonstrated that a higher proportion of patients receiving **CONSTELLA**® 290 mcg were responders versus placebo for the overall score and the 8 subscale scores (all $p<0.05$). Table 8 provides an overview of the IBS-QOL responder data from Trials 1 and 2.

Table 8: Quality of Life Results for CONSTELLA® in IBS-C (Responder Analyses, Pooled ITT Population)

IBS-QOL Parameter	CONSTELLA® 290 mcg N=805	Placebo N=797	CONSTELLA® 290 mcg N=805	Placebo N=797
	% of Patients with ≥10 point improvement		% of patients with ≥14 point improvement	
IBS-QOL Overall Score	64.3%[d]	52. 5%	53.8%[d]	39.0%
Dysphoria	62.0%[b]	53.6%	56.2%[d]	45.7%
Body Image	71. 7%[d]	59.5%	62.1%[d]	43.2%
Health Worry	67.6%[d]	56.1%	67.6%[d]	56.1%
Food Avoidance	57.4%[d]	46.6%	57.4%[d]	46.6%
Social Reaction	52.5%[b]	44. 5%	42.4%[c]	32.9%
Sexual	54.2%[c]	44.4%	37.9%[d]	26.9%
Relationships	41.6%[b]	34.7%	41.6%[b]	34.7%
Interference with Activity	54.7%[a]	48.5%	47.5%[b]	39.0%

[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, [d] $p<0.0001$(vs. placebo, CMH test)
IBS-QOL=Irritable Bowel Syndrome-Quality of Life

Chronic Idiopathic Constipation (CIC)

Study Demographics and Trial Design

The efficacy of **CONSTELLA®** for the treatment of CIC was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients (Trials 3 and 4). A total of 642 patients in Trial 3 and 630 patients in Trial 4 received treatment with the recommended 145 mcg dose of **CONSTELLA®**, the 290 mcg dose of **CONSTELLA®**, or placebo once daily, and were evaluated for efficacy. A summary of trial designs and patient demographics is presented in Table 9 below. In the two pivotal trials, 76% of patients were White, 22% were Black, and 10% were Hispanic.

The efficacy of the 72 mcg dose (Trial 5) was established by using a 12-week CSBM Overall Responder endpoint that was the same as in Trials 3 and 4.

Table 9: Summary of Patient Demographics for Clinical Trials Supporting Efficacy of CONSTELLA® in the Treatment of CIC (ITT Population)

Trial #	Trial Design/Duration	Oral Dosage	Study Subjects (N) [Female/Male (F/M)]	Mean Age (Range)	Mean Baseline Characteristics
3	12-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group Plus 4-week randomized withdrawal (RW) period	**CONSTELLA®** 145 mcg or 290 mcg once daily	N=642 [F=561; M=81]	48.0 (18-85)	CSBMs/week: 0.3 (0.0-2.9)
4	12-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group	**CONSTELLA®** 145 mcg or 290 mcg once daily	N=630 [F=570; M=60]	47.6 (20-83)	CSBMs/week: 0.3 (0.0-2.4)
5	12-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group	**CONSTELLA®** 72 mcg or 145 mcg once daily	N = 1223 [F = 942; M = 281]	46.0 (18 – 90)	CSBMs/week 0.2 (0.0 – 2.9)

CSBM=Complete Spontaneous Bowel Movement

All patients met modified Rome II criteria (Trials 3 and 4) or Rome III criteria (Trial 5) for functional constipation. Modified Rome II criteria were less than 3 spontaneous bowel movements (SBMs) per week and 1 of the following symptoms for at least 12 weeks, which need not be consecutive, in the preceding 12 months (Rome II) or with onset at least 6 months before diagnosis (Rome III):

- Straining during greater than 25% of bowel movements
- Lumpy or hard stools during greater than 25% of bowel movements
- Sensation of incomplete evacuation during greater than 25% of bowel movements

Patients were also required to have less than 3 complete spontaneous bowel movements (CSBMs) per week and less than or equal to 6 SBMs per week during a 2-week baseline period. Patients were excluded if they met criteria for IBS-C or had fecal impaction that required emergency room treatment.

The trial designs were identical through the first 12 weeks. Trial 3 also included an additional 4-week randomized withdrawal (RW) period. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take bismuth, prokinetic

agents, or other drugs to treat chronic constipation including laxatives (except for bisacodyl, the protocol-specified rescue medication).

Study Results

Trials 3 and 4

Efficacy of **CONSTELLA**® was assessed using overall responder analysis (primary endpoint) and change-from-baseline analyses (secondary endpoints). Results for endpoints were based on information provided daily by patients in electronic diaries, via an interactive voice response system.

Both doses of **CONSTELLA**® were statistically superior to placebo for the primary and secondary endpoints in each pivotal trial, with no incremental benefit of the 290 mcg dose over the 145 mcg dose. Therefore, the 145 mcg dose is the recommended dose.

Primary Endpoint

The primary efficacy endpoint was the proportion (%) of patients who had at least 3 CSBMs and an increase of at least 1 CSBM from baseline in a given week for at least 9 weeks out of the 12-week treatment period.

In the two pivotal trials (Trials 3 and 4), **CONSTELLA**® demonstrated statistically superior benefits, for the primary endpoint, compared to placebo in the treatment of CIC. In both trials, the proportion of patients who were CSBM responders was statistically significantly greater with **CONSTELLA**® than with placebo. Results are summarized in Tables 10 and 11.

Table 10: Trial 3 - Primary Efficacy of CONSTELLA® in CIC (ITT Population)

	Trial 3				
	Placebo (N=209)	**CONSTELLA® 145 mcg (N=217)**	**Treatment Difference [95% CI]**	**CONSTELLA® 290 mcg (N=216)**	**Treatment Difference [95% CI]**
CSBM Responder (≥ 3 CSBMs and Increase ≥ 1 CSBM from Baseline)	3.3%	21.2%[a]	17.8% [11.9%, 23.8%]	19.4%[a]	16.1% [10.3%, 21.9%]

[a] p<0.0001
CI=Confidence Interval, CSBM=Complete Spontaneous Bowel Movement

Table 11: Trial 4 - Primary Efficacy of CONSTELLA® in CIC (ITT Population)

	Trial 4				
	Placebo (N=215)	**CONSTELLA®14 5 mcg (N=213)**	**Treatment Difference [95% CI]**	**CONSTELLA® 290 mcg (N=202)**	**Treatment Difference [95% CI]**
CSBM Responder[a,b] (≥ 3 CSBMs and Increase ≥ 1 CSBM from Baseline)	6.0%	16.0%[a]	9.9% [4.1%, 15.8%]	21.3%[b]	15.2% [8.8%, 21.7%]

[a] $p \leq 0.05$, [b] $p < 0.0001$
CI=Confidence Interval, CSBM=Complete Spontaneous Bowel Movement

Secondary Endpoints

The secondary efficacy endpoints were the change from baseline in 12-week CSBM and SBM frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and constipation severity.

Patients who received **CONSTELLA®** across the 2 trials demonstrated statistically significantly greater improvements compared with patients receiving placebo for all secondary endpoints, including change from baseline in 12 week CSBM and SBM frequency, stool consistency (as measured by the Bristol Stool Form Scale (BSFS)), severity of straining, abdominal discomfort, bloating and constipation severity (Tables 12 and 13).

CSBM frequency reached maximum level during Week 1 and was also demonstrated over the remainder of the 12-week treatment period in Trial 3 and Trial 4. For the mean change from baseline in CSBM frequency at Week 12, the difference between placebo and **CONSTELLA®** was approximately 1.5 CSBMs.

Table 12: Trial 3 - Secondary Efficacy of CONSTELLA® in CIC (Mean Change from Baseline, ITT Population)

12-Week Parameter	Placebo (N=209)	CONSTELLA® 145 mcg (N=217)	LSMD (95% CI)	CONSTELLA® 290 mcg (N=216)	LSMD (95% CI)
CSBMs/week	0.5	1.9[c]	1.5 (1.0, 1.9)	2.0[c]	1.6 (1.2, 2.0)
SBMs/week	1.1	3.0[c]	2.0 (1.4, 2.5)	3.0[c]	1.9 (1.4, 2.5)
Stool Consistency*	0.6	1.9[c]	1.3 (1.1, 1.5)	1.8[c]	1.3 (1.0, 1.5)
Severity of Straining**	-0.5	-1.1[c]	-0.6 (-0.7, -0.5)	-1.2[c]	-0.6 (-0.8, -0.5)
Abdominal Discomfort**	-0.3	-0.5[b]	-0.2 (-0.3, -0.1)	-0.4[a]	-0.1 (-0.2, 0.0)
Bloating**	-0.2	-0.5[c]	-0.2 (-0.3, -0.1)	-0.4[a]	-0.2 (-0.3, -0.1)
Constipation Severity**	-0.3	-0.9[c]	-0.6 (-0.8, -0.5)	-0.8[c]	-0.5 (-0.7, -0.4)

[a] $p \leq 0.05$, [b] $p < 0.001$, [c] $p < 0.0001$
*BSFS Score, **5-point Ordinal Scale
BSFS=Bristol Stool Form Scale, CI=Confidence Interval, CSBM=Complete Spontaneous Bowel Movement, LSMD=Least Squares Mean Difference, SBM=Spontaneous Bowel Movement

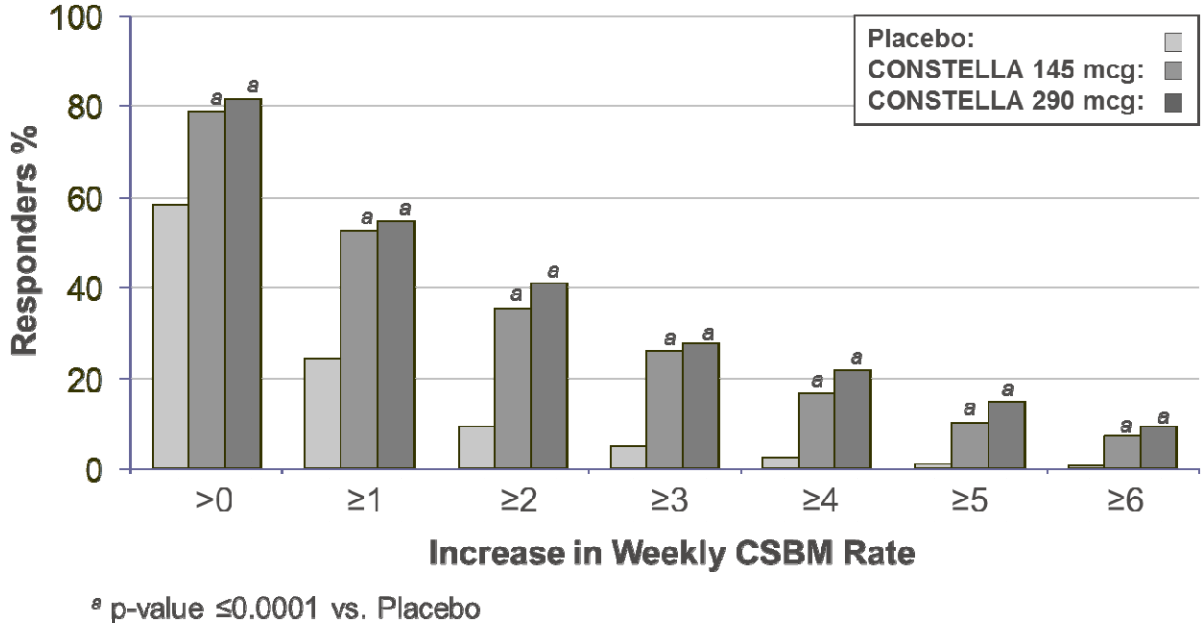
Table 13: Trial 4 - Secondary Efficacy of CONSTELLA® in CIC (Mean Change from Baseline, ITT Population)

12-Week Parameter	Placebo (N=215)	CONSTELLA® 145 mcg (N=213)	LSMD (95% CI)	CONSTELLA® 290 mcg (N=202)	LSMD (95% CI)
CSBMs/week	0.6	2.0[b]	1.4 (0.9, 1.9)	2.7[b]	2.0 (1.5, 2.6)
SBMs/week	1.1	3.4[b]	2.3 (1.7, 3.0)	3.7[b]	2.6 (1.9, 3.2)
Stool Consistency*	0.6	1.8[b]	1.3 (1.0, 1.5)	2.0[b]	1.4 (1.2, 1.7)
Severity of Straining**	-0.6	-1.1[b]	-0.6 (-0.7, -0.4)	-1.2[b]	-0.7 (-0.8, -0.5)
Abdominal Discomfort**	-0.3	-0.5[a]	-0.2 (-0.3, -0.1)	-0.5[b]	-0.2 (-0.3, -0.1)
Bloating**	-0.2	-0.4[a]	-0.2 (-0.3, -0.1)	-0.5[b]	-0.3 (-0.4, -0.1)
Constipation Severity**	-0.3	-0.9[b]	-0.6 (-0.8, -0.5)	-1.0[b]	-0.6 (-0.8, -0.5)

[a] $p<0.001$, [b] $p<0.0001$
*BSFS Score, **5-point Ordinal Scale
BSFS=Bristol Stool Form Scale, CI=Confidence Interval, CSBM=Complete Spontaneous Bowel Movement, LSMD=Least Squares Mean Difference, SBM=Spontaneous Bowel Movement

The proportions of patients who met response criteria of increasing levels of stool frequency compared to baseline (i.e., increases of >0, ≥1, ≥2, ≥3, ≥4, ≥5, and ≥6 CSBMs per week) over 12 weeks of treatment were analyzed. At each level, a statistically significantly greater proportion of patients treated with either dose of **CONSTELLA®** met the response criterion compared with placebo patients (Figure 3).

Figure 3: Percentage of CIC Patients with Incremental Increases in CSBM Frequency (Trials 3 & 4, Pooled ITT Population)

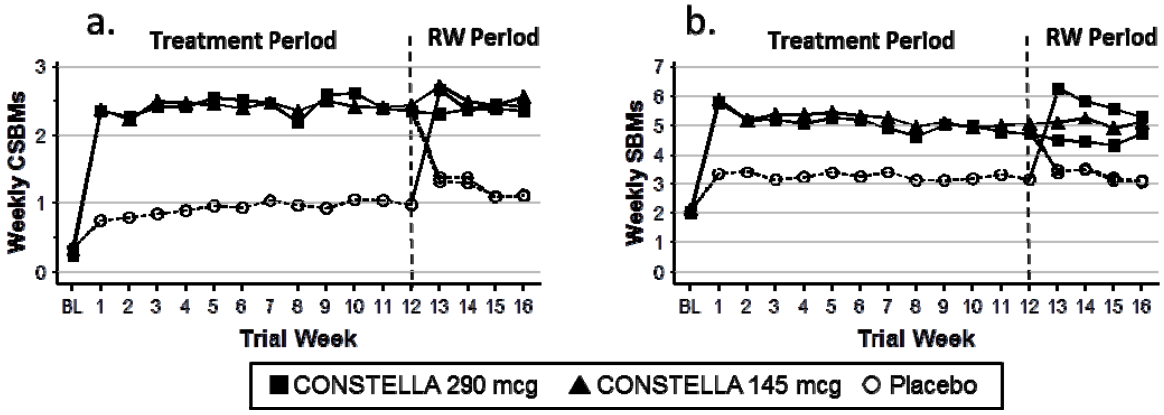


p≤0.0001 for all comparisons of linaclotide vs placebo
CSBM=Complete Spontaneous Bowel Movement

For CSBM and SBM frequency, each dose of **CONSTELLA®** demonstrated a statistically significant separation from placebo that was present at the first week and sustained across the 12 weeks of the treatment period ($p < 0.001$ for each dose vs. placebo at all time-points) for both trials.

During the 4-week randomized withdrawal period in Trial 3, patients who received **CONSTELLA®** during the 12-week treatment period were re-randomized to receive placebo or continue treatment on the same dose of **CONSTELLA®** taken during the treatment period. In **CONSTELLA®**-treated patients re-randomized to placebo, CSBM and SBM frequency returned toward baseline within 1 week with no evidence of rebound worsening compared to baseline. Patients who continued on **CONSTELLA®** maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to **CONSTELLA®** had an increase in CSBM and SBM frequency similar to the levels observed in patients taking **CONSTELLA®** during the treatment period (Figure 4).

Figure 4: Trial 3 - Mean (a) CSBM and (b) SBM Frequency by Week Over the 12-week Treatment Period and 4-week Randomized Withdrawal Period



CSBM=Complete Spontaneous Bowel Movement, SBM=Spontaneous Bowel Movement

Quality of Life Assessment

The Patient Assessment of Constipation – Quality of Life (PAC-QOL) instrument was utilized in the Phase 3 pivotal trials to assess the impact of constipation on a patient's quality of life. The PAC-QOL evaluated 4 dimensions: physical discomfort, psychosocial discomfort, worries/concerns, and satisfaction on a 0 to 4 point scale. A pooled analysis of the PAC-QOL data at Week 12 demonstrated that a higher proportion of patients receiving **CONSTELLA®** 145 mcg or **CONSTELLA®** 290 mcg were responders versus placebo for the overall score and the 4 subscale scores (all $p<0.05$). Table 14 provides an overview of the pooled PAC-QOL responder data from Trials 3 and 4.

Table 14: Quality of Life Results for CONSTELLA® in CIC (Responder Analyses, Pooled ITT Population)

PAC-QOL Parameter	CONSTELLA® 145 mcg N=430	CONSTELLA® 290 mcg N=418	Placebo N=423
	% of Patients with ≥1 point improvement		
PAC-QOL Overall Score	43.6%[b]	41.0%[b]	23.4%[b]
Satisfaction	53.8%[b]	52.3%[b]	28.3%[b]
Physical Discomfort	55.4%[b]	54.6%[b]	30.8%[b]
Worries/Concerns	48.1%[b]	45.1%[b]	26.7%[b]
Psychosocial Discomfort	24.7%[a]	29.1%[b]	18.6%[b]

[a] $p\leq0.05$, [b] $p<0.0001$(vs. placebo, CMH test)
PAC-QOL=Patient Assessment of Constipation-Quality of Life

72 mcg Trial (Trial 5)

The efficacy of the 72 mcg dose was established by using a 12-week CSBM Overall Responder endpoint that was the same as in Trials 3 and 4. In addition, to assess whether response was

sustained over time, a separate analysis (CSBM Sustained Responder) was performed, where responders were both a 12-week Overall Responder and a CSBM weekly responder for at least 3 of the last 4 weeks of the treatment period.

The response rates for the CSBM Overall Responder endpoint were 13.4% for **CONSTELLA**® 72 mcg 12.4% for **CONSTELLA**® 145 mcg and 4.7% for placebo. Results for the 12-week CSBM Sustained Responder were 12.4% for **CONSTELLA**® 72 mcg, 11.2% for **CONSTELLA**® 145 mcg and 4.7% for placebo.

DETAILED PHARMACOLOGY

Animal Pharmacology

In vitro pharmacodynamics

Several competitive binding studies were conducted using radiolabled pSTa (*E. coli* heat-stable enterotoxin derived from a porcine source) to confirm the molecular target of linaclotide and characterize its binding to guanylate cyclase-C (GC-C). Linaclotide and its active primary metabolite, MM-419447, each bound with similar high affinities to human colon carcinoma T84 cells, which are known to express high levels of GC-C. The binding was found to be pH-independent. Linaclotide bound to rat intestinal epithelial cells and brush-border membranes with high affinity, providing further evidence that linaclotide binds to GC-C. A study using intestinal mucosal membranes from wild-type (WT) and GC-C knock-out (KO) mice showed high affinity binding of linaclotide to GC-C in intestinal mucosal membranes from WT mice, but not those from GC-C KO mice, confirming that the GC-C is the molecular target of linaclotide.

Upon binding to GC-C, both linaclotide and its active metabolite stimulate the production of cGMP intracellularly, in a concentration-dependent manner, with similar minimal effective concentrations in human T84 cells. In human colonic adenocarcinoma (Caco-2) cell monolayers, linaclotide increased intracellular cGMP and induced both basolateral (submucosal) and apical (lumenal) cGMP efflux. This bidirectional cGMP efflux was inhibited by several known efflux transporter inhibitors, demonstrating that intracellular cGMP is actively transported out from intestinal epithelial cells.

In vivo pharmacodynamics

The pharmacological activities of linaclotide and MM-419447 have been characterized in a number of studies in rodent models of intestinal secretion, GI transit, and visceral pain. Linaclotide and MM-419447 stimulated a significant, dose-dependent increase in intestinal secretion in suckling mice with equal potency at a minimal effective dose of 2.5 mcg /kg. In adult mice and rats, using a loop-ligation assay, linaclotide stimulated a significant increase in intestinal fluid secretion, accompanied by a significant increase in luminal cGMP secretion. The effect of linaclotide on intestinal fluid and cGMP secretion is GC-C dependent since the effect was only observed in WT mice, but not in GC-C KO mice.

In mice, linaclotide at oral doses of 25 mcg /kg (single dose) and 60 mcg /kg, QD (5-day repeat dosing) significantly induced GI transit in WT mice, but not in GC-C KO mice. In Sprague-

Dawley rats, both linaclotide at 6.25 mcg /kg, p.o. and MM-419447 at 12.5 mcg/kg, p.o. produced a significant increase in GI transit.

In addition to its effect on intestinal secretion and GI transit, linaclotide significantly reduced visceral hypersensitivity. In a model of trinitrobenzene sulfonic acid (TNBS)-induced visceral hypersensitivity in WT mice linaclotide (0.01 mcg /kg, p.o.) reduced visceral hyperalgesia but had no effect in GC-C KO mice. In models of both inflammation- and stress-induced (i.e., partial restraint, water avoidance) visceral hyperalgesia in rats, linaclotide produced antinociceptive effects, without affecting the colonic tone. However, a clear dose-response relationship was not observed.

Safety pharmacology
Linaclotide tested at 10 and 100 μM concentrations exhibited negligible and not statistically significant inhibition (10 μM = 3.7% ± 2.0%; 100 μM = 0.9 ± 0.8%; vehicle = 0.7 ± 0.3%) of the human ether-a-go-go-related gene (hERG) channel current when tested *in vitro* in stably transfected human embryonic kidney (HEK) cells. In an *in vivo* safety pharmacology study, linaclotide did not produce any noticeable adverse respiratory or cardiovascular effects in dogs after administration of intravenous doses of up to 5 mg/kg.

Animal pharmacokinetics
Following oral dosing, linaclotide is minimally absorbed in all studied species, including mice, rats, and monkeys, with a low absolute oral bioavailability (≤ 0.2%).

While the predominant mechanism of clearance of orally administered linaclotide and its active primary metabolite is through proteolytic degradation in the lumen of the intestine, fecal recovery studies in rats have shown that a small amount of active peptide (≤ 1%), predominately in the form of the active metabolite, is excreted in the feces. These results also demonstrate that despite early rapid metabolism and degradation of linaclotide and MM-419447 in the proximal small intestine, some active peptide is available to interact with GC-C throughout the entire intestinal tract, including the colon.

Although very little active peptide is absorbed into systemic circulation after oral administration, when given intravenously in rats, both linaclotide and MM-419447 are rapidly cleared by at least two pathways. The kidney is a major clearance organ for systemically circulating linaclotide and MM-419447, and studies have indicated the presence of additional, non-renal pathways of clearance, including biliary clearance.

Human Pharmacology

Pharmacodynamics
Orally administered linaclotide acts on the luminal surface of the intestine. The pharmacodynamics of orally administered linaclotide was evaluated in healthy subjects and patients through bowel symptom assessments of stool, severity of straining associated with bowel movements, stool frequency, and stool weight. Because the form of the feces largely

depends on the time spent in the colon (i.e., slower transit results in harder stool form), stool consistency is a surrogate for GI transit. Single (29 mcg to 2897 mcg) and repeated once daily doses (29 mcg to 966 mcg) of linaclotide softened stools and decreased straining with bowel movements in healthy subjects relative to placebo, with more profound effects noted following doses ≥ 290 mcg.

In a food-effect study, healthy subjects treated for seven days with once-daily linaclotide (290 mcg) administered after a high-fat breakfast had looser stools and increased stool frequency compared with fasted patients, suggesting that food increases the pharmacodynamic effect of linaclotide.

Oral administration of linaclotide (97 mcg or 966 mcg) for five days to IBS-C patients, softened stools, increased stool frequency, improved ease of passage, and decreased time to first bowel movement, with a dose-dependent response for stool consistency. In addition to its effects on bowel movement parameters in these IBS-C patients, linaclotide was found to increase colonic transit using radiographic techniques.

Pharmacokinetics

Plasma concentrations of linaclotide and its active primary metabolite, MM-419447, were not generally measurable in humans, following oral administration of linaclotide, as expected for a peptide with a low permeability profile. There were no detectable plasma concentrations of linaclotide or MM-419447 in > 99% of linaclotide-dosed participants whose plasma was analyzed during clinical trials, regardless of participant gender, age, or race. Consequently, standard PK parameters could not be calculated for linaclotide or MM-419447.

While the predominant mechanism of clearance of orally administered linaclotide and its active primary metabolite is through proteolytic degradation in the intestine, fecal recovery studies in humans have shown that a small amount of active peptide, predominately in the form of the metabolite, is excreted in the feces (≤ 6%). These results also demonstrate that despite the early rapid metabolism and degradation of linaclotide and MM-419447 in the proximal small intestine, some active peptide is available to interact with GC-C throughout the entire intestinal tract, including the colon.

No clinical studies assessing drug-drug interactions were conducted. Linaclotide has a low permeability coefficient in Caco-2 cells and is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes. At clinically relevant concentrations, linaclotide is not a substrate for P-glycoprotein (P-gp) and does not inhibit common efflux and uptake transporters, including P-gp. The observed minimal systemic exposure to linaclotide and MM-419447 following oral administration of linaclotide, the extensive metabolism of both peptides within the GI tract, and the lack of interaction with common drug-transporting and drug-metabolizing enzymes have led to the conclusion that linaclotide is unlikely to interact with concomitantly administered medications.

TOXICOLOGY

Single-dose Toxicity

In rats, there was no detectable systemic exposure to linaclotide at single oral dose levels of up to 5.0 mg/kg (lower limit of quantitation [LLOQ] was 3 ng/mL). There were no linaclotide-related effects observed on survival, body weight, food consumption, clinical observations, or macroscopic evaluations. The No-Observed-Adverse-Effect-Level (NOAEL) was determined to be ≥ 5.0 mg/kg in rats (both sexes) given linaclotide as a single oral dose.

Cynomolgus monkeys were administered a single oral dose of linaclotide at dose levels of 0.5, 1.5, 3.0, and 5.0 mg/kg. Monkeys receiving a single oral dose ≥ 1.5 mg/kg exhibited changes in stool consistency (non-formed and/or liquid feces), qualitatively reduced food consumption, and/or abdominal distention. There were no significant changes in individual body weight data for these animals. A monkey dosed orally for five consecutive days at 1.5 mg/kg/day exhibited non-formed and liquid feces over the course of the dosing period, with mild abdominal distention occurring on the fourth dosing day. These results demonstrated that linaclotide was well tolerated by Cynomolgus monkeys following a single oral dose at dose levels up to 5.0 mg/kg. Clinical signs related to the exaggerated pharmacological effects of linaclotide on stool consistency were observed at oral doses of ≥ 1.5 mg/kg/day.

Repeat-dose Toxicity

Repeated-dose studies of orally administered linaclotide have been conducted in mice, rats and monkeys. In Good Laboratory Practice (GLP) two-week repeated-dose oral toxicity studies in rats and monkeys, the administration of linaclotide at dose levels of 20 mg/kg/day in rats and 5 mg/kg/day in monkeys was associated with no noteworthy findings in rats and reversible changes in stool consistency in monkeys. In a GLP 7-day repeated-dose intravenous toxicity study in monkeys, the administration of linaclotide at a dose level of 15 mg/kg/day was associated with stool consistency changes.

In GLP repeated-dose oral toxicity studies in rats and monkeys, linaclotide did not produce findings considered to be adverse when administered for up to 13 weeks at doses up to 100 mg/kg/day in rats and up to 5 mg/kg/day in monkeys. Reversible changes in stool consistency were observed in monkeys and are the exaggerated pharmacological effect of linaclotide. During a GLP 13-week repeated-dose oral toxicity study in mice, mortality related to linaclotide administration was observed at dose levels ≥ 100 mg/kg/day. Linaclotide-related microscopic changes were noted in the lymphoid system (spleen and thymus), GI tract (stomach, cecum), kidney, and heart at doses ≥ 100 mg/kg/day in both males and females. The no-observed-adverse-effect-level (NOAEL) for linaclotide in mice was 20 mg/kg/day administered orally once daily for 13 weeks.

Based upon the increased sensitivity of mice to linaclotide administration, mice were chosen as the species for the GLP 26-week repeated-dose oral toxicity study in rodents. In the 26-week toxicity study, mortality was observed early in the study in the high dose (100/80 mg/kg/day) group. However, no linaclotide-related clinical pathology changes, gross or microscopic findings were noted at any dose level in either sex. Based on the mortality observed, the NOAEL was

20 mg/kg/day in mice administered linaclotide orally for 26 weeks.

In the GLP 39-week study in monkeys, changes in stool consistency (watery feces) were present at all dose levels evaluated in both sexes and were consistent with the exaggerated pharmacological effects of linaclotide. Repeated daily oral dosing for up to 39 weeks did not result in any apparent decrease in the pharmacological effects of linaclotide on stool consistency during the dosing interval and the effects on stool consistency were reversible upon discontinuation of dosing. Two monkeys (one male in the mid dose group and one female in the high dose group) were euthanized moribund due to severe watery feces (e.g., diarrhea) and associated progressive dehydration. Mortality in these monkeys was considered to be related to exaggerated pharmacology of linaclotide. Clinical observations and histopathologic findings in the large intestine (colon, cecum and rectum) identified the GI system as target organs in both animals euthanized moribund. In other animals in this study which survived until scheduled necropsy, there were no linaclotide-related clinical pathology changes, nor any gross or microscopic findings. Based on mortality, the NOAEL was determined to be 5 mg/kg/day in monkeys administered linaclotide orally for 39 weeks.

Genotoxicity
Linaclotide was not genotoxic in an *in vitro* bacterial reverse mutation (Ames) assay or in the *in vitro* chromosomal aberration assay in cultured human peripheral blood lymphocytes.

Carcinogenicity
In 2-year carcinogenicity studies, linaclotide was not tumorigenic in rats at doses up to 3,500 mcg/kg/day or in mice at doses up to 6,000 mcg/kg/day.

Reproductive and Developmental Toxicity
Linaclotide had no effect on fertility or reproductive function in male and female rats at oral doses of up to 100 mg/kg/day.

Studies in Juvenile Animals: In a range-finding tolerability study, when administered orally for 5 days, linaclotide was tolerated at higher dose levels in juvenile mice when treatment was initiated on Day 21 post-partum compared to Day 14 or Day 7. In mice, younger animals were more sensitive to linaclotide-related mortality. In the definitive GLP 9-week repeated-dose oral toxicity study in juvenile mice initiated on Day 7 post-partum, there was an increase in mortality after administration of 1 or 2 doses of linaclotide at 10 mcg/kg/day through Day 9 post-partum. However the 10 mcg/kg/day dose level was well tolerated after Day 9 post-partum for the remaining treatment period in surviving juvenile mice, with no linaclotide-related adverse effects or microscopic findings and no effects on the physical development or neurobehavioral assessments. Based on the mortality observed, the NOAEL was determined to be 3 mcg/kg/day in juvenile mice administered linaclotide orally once daily for 9 weeks. The increased sensitivity of juvenile mice to linaclotide may be related to the increased expression of intestinal GC-C receptors in young animals or possibly other factors such as those related to an immature GI system [see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, Special Populations, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Teratology Studies

The potential for linaclotide to cause teratogenic effects was studied in rats, rabbits and mice. Oral administration of up to 100 mg/kg/day in rats and 40 mg/kg/day in rabbits produced no maternal toxicity and no effects on embryo-fetal development. In mice, oral dose levels of at least 40 mg/kg/day produced severe maternal toxicity including death, reduction of gravid uterine and fetal weights, and effects on fetal morphology. Oral doses of 5 mg/kg/day did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice.

REFERENCES

1. Andresen V, Camilleri M, Busiglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology 2007; 133: 761-8.

2. Chey WD, Lembo AJ, Lavins BJ et al. Linaclotide for Irritable Bowel Syndrome with Constipation: A 26-week, Randomized, Double-blind, Placebo-controlled Trial to Evaluate Efficacy and Safety. American Journal of Gastroenterology (in press).

3. Johnston JM, Kurtz CB, MacDougall JE et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 2010; 139: 1877-86.

4. Lembo AJ, Kurtz CB, MacDougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology 2010; 138:886-95.

5. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. NEJM 2011; 365: 527-36.

6. Quigley EM, Tack J, Chey WD et al. Randomised Clinical Trials: Linaclotide Phase 3 Studies in IBS-C - a Prespecified Further Analysis Based On European Medicines Agency-Specified Endpoints. Aliment Pharmacol Ther 2013;37:49-61.

7. Rao S, Lembo AJ, Shiff SJ et al. A 12-Week, Randomized, Controlled Trial with a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome with Constipation. American Journal of Gastroenterology. Am J Gastroenterol 2012;107:1714-1724.

PART III: CONSUMER INFORMATION

PrCONSTELLA®
Linaclotide Capsules

This leaflet is part III of a three-part "Product Monograph" published when CONSTELLA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CONSTELLA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for in adults:
CONSTELLA® has been prescribed to you by your doctor to treat your:

- Irritable bowel syndrome with constipation (IBS-C).
- Chronic idiopathic constipation (CIC). "Idiopathic" means the cause of the constipation is unknown.

What it does:
CONSTELLA® is a medication in a class called guanylate cyclase type C (GC-C) agonist. **CONSTELLA®** is believed to relieve constipation by adding fluid to the bowels, making bowel movements (BMs) softer, and helping them occur more often. It is also believed to decrease abdominal pain by acting on pain-sensing nerves in the intestines.

IBS-C
IBS-C is a bowel disorder in which abdominal (stomach area) symptoms, including pain, discomfort and bloating are experienced along with constipation. **CONSTELLA®** may help you feel less pain, discomfort, and bloating in your abdomen. It may also help your constipation by causing you to have more BMs, softer BMs, and less straining to pass the BM. You may notice improvement of bowel symptoms within the first week; the pain or discomfort in your abdomen may take longer to improve.

CIC
CIC is a bowel disorder with many bowel and abdominal symptoms including constipation, straining, hard stools, discomfort, bloating and a sense of incomplete BM. **CONSTELLA®** may help you have more BMs, softer BMs, and less straining to pass the BM. You may also feel less discomfort and bloating in your abdomen. You may notice improvement of bowel symptoms within the first week.

CONSTELLA® may help your IBS-C or CIC symptoms, but **CONSTELLA®** is not a cure for either condition. If you stop taking **CONSTELLA®**, your symptoms may return within 1 week.

When it should not be used:
Do not give **CONSTELLA®** to children under 6 years of age.
Do not take **CONSTELLA®** if:

- you are allergic to it or any of the other ingredients in **CONSTELLA®** or component of the container (see **What the nonmedicinal ingredients are** section).
- a doctor has told you recently that you have a bowel blockage (intestinal obstruction).

What the medicinal ingredient is:
linaclotide

What the nonmedicinal ingredients are:
Nonmedicinal ingredients for the 145 mcg and 290 mcg capsules include: calcium chloride dihydrate, gelatin, hypromellose, iron oxide black, iron oxide yellow, L-leucine, microcrystalline cellulose, shellac glaze, and titanium dioxide.

Nonmedicinal ingredients for the 72 mcg capsules include: calcium chloride dihydrate, gelatin, L-histidine, iron oxide black, iron oxide yellow, microcrystalline cellulose, polyvinyl alcohol, shellac glaze, talc, titanium dioxide.

What dosage forms it comes in:
CONSTELLA® comes in 3 capsule strengths: 72 mcg, 145 mcg and 290 mcg.

WARNINGS AND PRECAUTIONS

Read this information before you start taking **CONSTELLA®** and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

If you have any questions about **CONSTELLA®**, ask your doctor.

CONSTELLA® must not be used in children under 6 years of age and is not recommended for use in children and adolescents between 6 and 18 years of age. The safety and efficacy of CONSTELLA® in children and adolescents (less than 18 years of age) have not been established.

BEFORE you use **CONSTELLA®** talk to your doctor or pharmacist if:

- You have any other medical conditions.
- You are pregnant, think you may be pregnant, or plan to become pregnant. It is not known if **CONSTELLA®** will harm your unborn baby.
- You are breast-feeding or planning to breastfeed. It is not known if **CONSTELLA®** passes into your breast milk. Talk with your doctor about the best way to feed your baby, if you take **CONSTELLA®**.
- You are taking or planning to take any other medicines, including prescription and non-prescription drugs, vitamins and herbal supplements.

INTERACTIONS WITH THIS MEDICATION

As very little linaclotide is absorbed from the intestines, no drug interaction studies have been conducted with **CONSTELLA®**.

Your doctor or pharmacist can tell you if it is safe to take

CONSTELLA® with your other medicines. Do not start or stop any medicine while taking **CONSTELLA®** without talking to your healthcare provider first.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:

- Take **CONSTELLA®** exactly as your doctor tells you to take it.
- Take **CONSTELLA®** one time each day on an empty stomach, at least 30 minutes before your first meal of the day.
- Swallow the capsule whole with water. Do not chew the capsule. Adults who have difficulty swallowing can open the capsules and sprinkle the contents over applesauce or mix the contents with water before swallowing.

It is not known if **CONSTELLA®** can be sprinkled with other foods or liquids.

To take with applesauce:

- Open the **CONSTELLA®** capsule and sprinkle all of the beads onto 1 teaspoon of room temperature applesauce.
- Swallow all of the **CONSTELLA®** beads and applesauce right away. Do not keep the applesauce for future use.
- Do not chew the **CONSTELLA®** beads.

To take with water:

- Open the **CONSTELLA®** capsule and pour all of the beads into a cup with 30 mL of room temperature bottled water.
- Gently swirl the beads and water for at least 20 seconds.
- Swallow all of the **CONSTELLA®** beads and water mixture right away. Do not keep the mixture for future use.
- Add another 30 mL of water to the cup, swirl for at least 20 seconds and swallow right away.

To take in a nasogastric or gastric feeding tube:

- Open the **CONSTELLA®** capsule and pour all of the beads into a cup with 30 mL of room temperature bottled water.
- Gently swirl the beads and water for at least 20 seconds.
- Draw-up the bead-water mixture into an appropriately sized catheter-tipped syringe. Your doctor should tell you the appropriate size for your dose.
- Remove the cap from the syringe, insert the tip of the syringe into the nasogastric tube or gastric feeding tube and push the plunger all the way in to give the dose.
- After giving the **CONSTELLA®** dose, flush the nasogastric or gastric tube with at least 10 mL of water.
- Add another 30 mL of water to the cup and repeat the process.
- The mixture of beads and water should be used right away. Do not keep for future use.

The first meal of the day can be consumed 30 minutes after dosing with **CONSTELLA®**.

Ask your doctor if you have any questions about how to give **CONSTELLA®** the right way.

If no improvement in symptoms is seen within 6 weeks, contact your doctor.

Overdose:

In case of drug overdose, contact a health care provider, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of **CONSTELLA®**, just skip that dose. Do not take two capsules to make up the missed dose. Instead, wait until the next time you are supposed to take it and then take your normal dose on an empty stomach, at least 30 minutes before your first meal of the day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects reported with **CONSTELLA®** are:

- Diarrhea
- Passing gas
- Abdominal (stomach-area) pain
- Swelling, or a feeling of fullness or pressure in your abdomen (bloating)
- Nausea
- Vomiting

Some side effects can be serious.

Mild to moderate diarrhea often begins within the first two weeks of taking **CONSTELLA®**. **Stop taking CONSTELLA® and call your doctor right away if you get severe diarrhea (for example persistent watery stools) during treatment with CONSTELLA®.**

Call your doctor or go to the nearest hospital emergency room right away, if you develop unusual or severe abdominal pain.

This is not a complete list of side effects. If you have other unexpected side effects, side effects that bother you or do not go away, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Uncommon	Severe diarrhea			√
Rare	New or worsening abdominal pain not typical of your IBS-C or CIC symptoms			√

HOW TO STORE IT

- Store **CONSTELLA®** at room temperature between 15ºC and 25ºC.
- Keep **CONSTELLA®** in the bottle that it comes in.
- The **CONSTELLA®** bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.
- Keep the container of **CONSTELLA®** tightly closed and in a dry place.

Keep CONSTELLA® and all medicines out of the sight and reach of children.

Do not use **CONSTELLA®** past the expiration date shown on the package.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This Consumer Information Leaflet provides you with the most current information at the time of printing. For the most current information, the Consumer Information Leaflet plus the full product monograph, prepared for health professionals can be found at:
http://www.allergan.ca
or by contacting the sponsor, Allergan Inc., at:
1-800-668-6424
This leaflet was prepared by Allergan Inc.

© 2018 Allergan. All Rights Reserved.

CONSTELLA® is a trademark of Ironwood Pharmaceuticals, Inc. used under license by Allergan Inc.

Last revised: August 28, 2018