

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202811Orig1s010

Trade Name: Linzess Capsules, 72 mcg.

***Generic or
Established:*** linaclotide

Sponsor: Forest Laboratories, LLC

Approval Date: July 23, 2018

Indication: New drug application proposes a new dosage regimen (72 mcg) for the treatment of adults with chronic idiopathic constipation (CIC).

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APPROVAL LETTER



NDA 202811/S-010

SUPPLEMENT APPROVAL

Forest Laboratories, LLC
Attention: Linda Kunka
Director, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Ms. Kunka:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 25, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Linzess (linaclotide) capsules, 72 mcg.

This Prior Approval supplemental new drug application proposes a new dosage regimen (72 mcg) for the treatment of adults with chronic idiopathic constipation (CIC).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your January 24, 2017, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 21, 2016, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

No new pediatric assessments are required because those already required for this NDA are sufficient. The following is a list of deferred required pediatric assessments which are applicable to this supplemental NDA approval for a new dosing regimen in adults with chronic idiopathic constipation:

2161-2 Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 2 to 5 years treated with Linzess (linaclotide).

Final Protocol Submission 01/18
Study Completion 12/22
Final Report Submission 12/23

2161-3 Conduct a safety and efficacy study in pediatric patients with chronic Idiopathic constipation ages 6 to 17 years treated with Linzess (linaclotide).

Final Protocol Submission 04/15
Study Completion 12/22
Final Report Submission 12/23

Submit the protocols to your IND 063290, with a cross-reference letter to this NDA.

Reports of this/these required pediatric postmarketing study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CDR Cheronda Cherry-France, Regulatory Project Manager, at (301) 796-7295.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.P.H., M.D.
Deputy Director, Safety
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
01/25/2017

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LINZESS safely and effectively. See full prescribing information for LINZESS.

LINZESS (linaclotide) capsules, for oral use
Initial U.S. Approval: 2012

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS
See full prescribing information for complete boxed warning.

- LINZESS is contraindicated in patients less than 6 years of age; in neonatal mice, linaclotide caused deaths due to dehydration. (4, 8.4)
- Avoid use of LINZESS in patients 6 years to less than 18 years of age. (5.1, 8.4)
- The safety and effectiveness of LINZESS have not been established in patients less than 18 years of age (8.4).

- Take on empty stomach at least 30 minutes prior to first meal of the day.
- Do not crush or chew LINZESS capsule or capsule contents.
- For patients who have difficulty swallowing capsules whole or those with a nasogastric or gastrostomy tube, see full prescribing information for instructions for opening the capsule and administering with applesauce or water.

-----**DOSAGE FORMS AND STRENGTHS**-----
Capsules: 72 mcg, 145 mcg and 290 mcg (3)

- CONTRAINDICATIONS**-----
- Patients less than 6 years of age due to the risk of serious dehydration. (4, 5.1, 8.4)
 - Patients with known or suspected mechanical gastrointestinal obstruction. (4)

- WARNINGS AND PRECAUTIONS**-----
- Diarrhea: Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate the patient. (5.2)

-----**ADVERSE REACTIONS**-----
Most common adverse reactions (≥2%) reported in IBS-C or CIC patients are: diarrhea, abdominal pain, flatulence and abdominal distension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2017

-----**RECENT MAJOR CHANGES**-----
Dosage and Administration (2.1) 01/2017
Warnings and Precautions (5.2) 08/2016

-----**INDICATIONS AND USAGE**-----
LINZESS is a guanylate cyclase-C agonist indicated in adults for treatment of:

- Irritable bowel syndrome with constipation. (IBS-C) (1)
- Chronic idiopathic constipation. (CIC) (1)

-----**DOSAGE AND ADMINISTRATION**-----
The recommended dosage in adults is:

- IBS-C: 290 mcg orally once daily. (2.1)
- CIC: 145 mcg orally once daily or 72 mcg orally once daily based on individual presentation or tolerability. (2.1)

Administration Instructions (2.2):

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Preparation and Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- LINZESS is contraindicated in patients less than 6 years of age; in nonclinical studies in neonatal mice, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration [see *Contraindications (4)*, *Use in Specific Populations (8.4)*].
- Avoid use of LINZESS in patients 6 years to less than 18 years of age [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.4)*].
- The safety and effectiveness of LINZESS have not been established in patients less than 18 years of age [see *Use in Specific Populations (8.4)*].

1 INDICATIONS AND USAGE

LINZESS is indicated in adults for the treatment of:

- irritable bowel syndrome with constipation (IBS-C)
- chronic idiopathic constipation (CIC).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Irritable Bowel Syndrome with Constipation (IBS-C)

The recommended dosage of LINZESS is 290 mcg orally once daily.

Chronic Idiopathic Constipation (CIC)

The recommended dosage of LINZESS is 145 mcg orally once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability.

2.2 Preparation and Administration Instructions

- Take LINZESS on an empty stomach, at least 30 minutes prior to the first meal of the day
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take 2 doses at the same time.
- Do not crush or chew LINZESS capsule or capsule contents.
- Swallow LINZESS capsule whole.
- For adult patients with swallowing difficulties, LINZESS capsules can be opened and administered orally in either applesauce or with water or administered with water via a nasogastric or gastrostomy tube. Sprinkling of LINZESS beads on other soft foods or in other liquids has not been tested.

Oral Administration in Applesauce:

1. Place one teaspoonful of room-temperature applesauce into a clean container.

2. Open the capsule.
3. Sprinkle the entire contents (beads) on applesauce.
4. Consume the entire contents immediately. Do not chew the beads. Do not store the bead-applesauce mixture for later use.

Oral Administration in Water:

1. Pour approximately 30 mL of room-temperature bottled water into a clean cup.
2. Open the capsule
3. Sprinkle the entire contents (beads) into the water
4. Gently swirl beads and water for at least 20 seconds.
5. Swallow the entire mixture of beads and water immediately.
6. Add another 30 mL of water to any beads remaining in cup, swirl for 20 seconds, and swallow immediately.
7. Do not store the bead-water mixture for later 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 the beads to deliver the complete dose.

Administration with Water via a Nasogastric or Gastrostomy Tube:

1. Open the capsule and empty the beads into a clean container with 30 mL of room-temperature bottled water.
2. Mix by gently swirling beads for at least 20 seconds
3. Draw-up the beads and 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.
4. Add another 30 mL of water to any beads remaining in the container and repeat the process
5. After administering the bead-water mixture, flush nasogastric/ gastrostomy tube with a minimum of 10 mL of water.

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

3 DOSAGE FORMS AND STRENGTHS

LINZESS capsules are white to off-white opaque:

- 72 mcg; gray imprint “FL 72”
- 145 mcg; gray imprint “FL 145”
- 290 mcg; gray imprint “FL 290”

4 CONTRAINDICATIONS

LINZESS is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [see *Warnings and Precautions (5.1), Use in Specific Populations (8.4)*]
- Patients with known or suspected mechanical gastrointestinal obstruction

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

LINZESS is contraindicated in patients less than 6 years of age. The safety and effectiveness of LINZESS in patients less than 18 years of age have not been established. In neonatal mice (human age equivalent of approximately 0 to 28 days), linaclotide increased fluid secretion as a consequence of GC-C agonism resulting in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.

Avoid use of LINZESS in pediatric patients 6 years to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of LINZESS in pediatric patients 6 years to less than 18 years of age [see *Contraindications (4)*, *Warnings and Precautions (5.2)*, *Use in Specific Populations (8.4)*].

5.2 Diarrhea

Diarrhea was the most common adverse reaction of LINZESS-treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. The incidence of diarrhea was similar between the IBS-C and CIC populations. Severe diarrhea was reported in 2% of 145 mcg and 290 mcg LINZESS-treated patients, and in <1% of 72 mcg LINZESS-treated CIC patients [see *Adverse Reactions (6.1)*].

In post-marketing experience, severe diarrhea associated with dizziness, syncope, hypotension and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or intravenous fluid administration have been reported in patients treated with LINZESS.

If severe diarrhea occurs, suspend dosing and rehydrate the patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Exposure in clinical development included approximately 2570, 2040, and 1220 patients with either IBS-C or CIC treated with LINZESS for 6 months or longer, 1 year or longer, and 18 months or longer, respectively (not mutually exclusive).

Demographic characteristics were comparable between treatment groups in all studies [see *Clinical Studies (14)*].

Irritable Bowel Syndrome with Constipation (IBS-C)

Most Common Adverse Reactions

The data described below reflect exposure to LINZESS in the two placebo-controlled clinical trials involving 1605 adult patients with IBS-C (Trials 1 and 2). Patients were randomized to receive placebo or 290 mcg LINZESS once daily on an empty stomach for up to 26 weeks. Table 1 provides the incidence of adverse reactions reported in at least 2% of IBS-C patients in the LINZESS treatment group and at an incidence that was greater than in the placebo group.

Table 1: Most Common Adverse Reactions^a in Two Placebo-Controlled Trials (1 and 2) in Patients with IBS-C

Adverse Reactions	LINZESS 290 mcg [N=807] %	Placebo [N=798] %
<i>Gastrointestinal</i>		
Diarrhea	20	3
Abdominal pain ^b	7	5
Flatulence	4	2
Abdominal distension	2	1
<i>Infections and Infestations</i>		
Viral Gastroenteritis	3	1
<i>Nervous System Disorders</i>		
Headache	4	3

^a: Reported in at least 2% of LINZESS-treated patients and at an incidence greater than placebo

^b: "Abdominal pain" term includes abdominal pain, upper abdominal pain, and lower abdominal pain.

Diarrhea

Diarrhea was the most commonly reported adverse reaction of the LINZESS-treated patients in the pooled IBS-C pivotal placebo-controlled trials. In these trials, 20% of LINZESS-treated patients reported diarrhea compared to 3% of placebo-treated patients. Severe diarrhea was reported in 2% of the LINZESS-treated patients versus less than 1% of the placebo-treated patients, and 5% of LINZESS-treated patients discontinued due to diarrhea vs less than 1% of placebo-treated patients. The majority of reported cases of diarrhea started within the first 2 weeks of LINZESS treatment [see *Warnings and Precautions (5.2)*].

Adverse Reactions Leading to Discontinuation

In placebo-controlled trials in patients with IBS-C, 9% of patients treated with LINZESS and 3% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LINZESS treatment group, the most common reasons for discontinuation due to adverse reactions were diarrhea (5%) and abdominal pain (1%). In comparison, less than 1% of patients in the placebo group withdrew due to diarrhea or abdominal pain.

Adverse Reactions Leading to Dose Reductions

In the open-label, long-term trials, 2147 patients with IBS-C received 290 mcg of LINZESS daily for up to 18 months. In these trials, 29% of patients had their dose reduced or suspended secondary to adverse reactions, the majority of which were diarrhea or other GI adverse reactions.

Less Common Adverse Reactions

Defecation urgency, fecal incontinence, vomiting, and gastroesophageal reflux disease were reported in <2% of patients in the LINZESS treatment group and at an incidence greater than in the placebo treatment group.

Chronic Idiopathic Constipation (CIC)

Most Common Adverse Reactions

The data described below reflect exposure to LINZESS in the two double-blind placebo-controlled clinical trials of 1275 adult patients with CIC (Trials 3 and 4). Patients were randomized to receive placebo or 145 mcg LINZESS or 290 mcg LINZESS once daily on an empty stomach, for at least 12 weeks. Table 2 provides the incidence of adverse reactions reported in at least 2% of CIC patients in the 145 mcg LINZESS treatment group and at an incidence that was greater than in the placebo treatment group.

Table 2: Most Common Adverse Reactions^a in the Two Placebo-controlled Trials (3 and 4) in Patients with CIC

Adverse Reactions	LINZESS 145 mcg [N=430] %	Placebo [N=423] %
<i>Gastrointestinal</i>		
Diarrhea	16	5
Abdominal pain ^b	7	6
Flatulence	6	5
Abdominal distension	3	2
<i>Infections and Infestations</i>		
Upper respiratory tract infection	5	4
Sinusitis	3	2

^a: Reported in at least 2% of LINZESS-treated patients and at an incidence greater than placebo

^b: "Abdominal pain" term includes abdominal pain, upper abdominal pain, and lower abdominal pain.

The safety of a 72 mcg dose was evaluated in an additional placebo-controlled trial in which 1223 patients were randomized to LINZESS 72 mcg, 145 mcg, or placebo once daily for 12 weeks (Trial 5).

In Trial 5, adverse reactions that occurred at a frequency of $\geq 2\%$ in LINZESS-treated patients (n=411 in each LINZESS 72 mcg and 145 mcg group) and at a higher rate than placebo (n=401) were:

- Diarrhea (LINZESS 72 mcg 19%; LINZESS 145 mcg 22%; placebo 7%)
- Abdominal distension (LINZESS 72 mcg 2%; LINZESS 145 mcg 1%; placebo < 1%)

Diarrhea

This section summarizes information from Trials 3 and 4 (pooled) and Trial 5 regarding diarrhea, the most commonly reported adverse reaction reported in LINZESS-treated patients in CIC placebo-controlled studies.

In all trials, the majority of reported cases of diarrhea started within the first 2 weeks of LINZESS treatment.

Severe diarrhea was reported in less than 1% of the 72 mcg LINZESS-treated patients (Trial 5), in 2% of the 145 mcg LINZESS-treated patients (Trials 3 and 4; Trial 5), and less than 1% of the placebo-treated patients (Trials 3, 4, and 5) [see *Warnings and Precautions (5.2)*].

Adverse Reactions Leading to Discontinuation

In placebo-controlled trials in patients with CIC, 3% of patients treated with 72 mcg (Trial 5) and between 5% (Trial 5) and 8% (Trials 3 and 4) of patients treated with 145 mcg of LINZESS discontinued prematurely due to adverse reactions compared to between less than 1% (Trial 5) and 4% (Trials 3 and 4) of patients treated with placebo.

In patients treated with 72 mcg LINZESS the most common reason for discontinuation due to adverse reactions was diarrhea (2% in Trial 5) and in patients treated with 145 mcg LINZESS, the most common reasons for discontinuation due to adverse reactions were diarrhea (3% in Trial 5 and 5% in Trials 3 and 4) and abdominal pain (1% in Trials 3 and 4). In comparison, less than 1% of patients in the placebo group withdrew due to diarrhea or abdominal pain (Trials 3 and 4; Trial 5).

Adverse Reactions Leading to Dose Reductions

In the open-label, long-term trials, 1129 patients with CIC received 290 mcg of LINZESS daily for up to 18 months. In these trials, 27% of patients had their dose reduced or suspended secondary to adverse reactions, the majority of which were diarrhea or other GI adverse reactions.

Less Common Adverse Reactions

Defecation urgency, fecal incontinence, dyspepsia, and viral gastroenteritis, were reported in less than 2% of patients in the LINZESS treatment group and at an incidence greater than placebo treatment group.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of LINZESS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hematochezia, rectal hemorrhage, nausea, and allergic reactions, urticaria or hives.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Linaclootide and its active metabolite are negligibly absorbed systemically following oral administration [see *Clinical Pharmacology (12.3)*], and maternal use is not expected to result in fetal exposure to the drug. The available data on LINZESS use in pregnant women are not sufficient to inform any drug-associated risk for major birth defects and miscarriage. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of linaclootide in rats and rabbits during organogenesis at doses much higher than the maximum recommended human dosage. Severe maternal toxicity associated with effects on fetal morphology were observed in mice [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

The potential for linaclootide to cause harm to embryo-fetal development was studied in rats, rabbits and mice. In pregnant mice, oral dose levels of at least 40,000 mcg/kg/day given during organogenesis produced severe maternal toxicity including death, reduction of gravid uterine and fetal weights, and effects on fetal morphology. Oral doses of 5,000 mcg/kg/day did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice. Oral administration of up to 100,000 mcg/kg/day in rats and 40,000 mcg/kg/day in rabbits during organogenesis produced no maternal toxicity and no effects on embryo-fetal development. Additionally, oral administration of up to 100,000 mcg/kg/day in rats during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation.

The maximum recommended human dose is approximately 5 mcg/kg/day, based on a 60-kg body weight. Limited systemic exposure to linaclootide was achieved in animals during organogenesis (AUC = 40, 640, and 25 ng•hr/mL in rats, rabbits, and mice, respectively, at the highest dose levels). Linaclootide and its active metabolite are not measurable in human plasma following administration of the recommended clinical dosages. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

8.2 Lactation

Risk Summary

There is no information regarding the presence of linaclootide in human milk, or on its effects on milk production or the breastfed infant. No lactation studies in animals have been conducted. Linaclootide and its active metabolite are negligibly absorbed systemically following oral administration [see *Clinical Pharmacology (12.3)*]. It is unknown whether the negligible systemic absorption of linaclootide by adults will result in a clinically relevant exposure to breastfed infants. Exposure to linaclootide in breastfed infants has the potential for serious adverse effects [see *Use in Specific Populations (8.4)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for

LINZESS and any potential adverse effects on the breastfed infant from LINZESS or from the underlying maternal condition.

8.4 Pediatric Use

LINZESS is contraindicated in patients less than 6 years of age. Avoid use of LINZESS in patients 6 years to less than 18 years of age [see *Contraindications (4), Warnings and Precautions (5.1)*]. The safety and effectiveness of LINZESS in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred within 24 hours in neonatal mice (human age equivalent of approximately 0 to 28 days) following oral administration of linaclotide, as described below in Juvenile Animal Toxicity Data. Because of increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop diarrhea and its potentially serious consequences. LINZESS is contraindicated in patients less than 6 years of age.

Given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of LINZESS in patients 6 years to less than 18 years of age.

Juvenile Animal Toxicity Data

In toxicology studies in neonatal mice, oral administration of linaclotide at 10 mcg/kg/day caused deaths on post-natal day 7 (human age equivalent of approximately 0 to 28 days). These deaths were due to rapid and severe dehydration produced by significant fluid shifts into the intestinal lumen resulting from GC-C agonism in neonatal mice [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Tolerability to linaclotide increases with age in juvenile mice. In 2-week-old mice, linaclotide was well tolerated at a dose of 50 mcg/kg/day, but deaths occurred after a single oral dose of 100 mcg/kg. In 3-week-old mice, linaclotide was well tolerated at 100 mcg/kg/day, but deaths occurred after a single oral dose of 600 mcg/kg.

8.5 Geriatric Use

Irritable Bowel Syndrome with Constipation (IBS-C)

Of 1605 IBS-C patients in the placebo-controlled clinical studies of LINZESS, 85 (5%) were 65 years of age and over, while 20 (1%) were 75 years and over. Clinical studies of LINZESS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Chronic Idiopathic Constipation (CIC)

Of 2498 CIC patients in the placebo-controlled clinical studies of LINZESS (Trials 3, 4, and 5), 273 (11%) were 65 years of age and over, while 56 (2%) were 75 years and over. Clinical studies of LINZESS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection

fluid and accelerated transit. In animal models, linaclotide has been shown to both accelerate GI transit and reduce intestinal pain.

In an animal model of visceral pain, linaclotide reduced abdominal muscle contraction and decreased the activity of pain-sensing nerves by increasing extracellular cGMP.

12.2 Pharmacodynamics

Food Effect

Taking LINZESS immediately after the high fat breakfast resulted in looser stools and a higher stool frequency compared with taking it in the fasted state [see *Dosage and Administration* (2.1, 2.2)]. In clinical trials, LINZESS was administered on an empty stomach, at least 30 minutes before breakfast.

12.3 Pharmacokinetics

Absorption

LINZESS is minimally absorbed with negligible systemic availability following oral administration. Concentrations of linaclotide and its active metabolite in plasma are 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.

Food Effect

Neither linaclotide nor its active metabolite were detected in the plasma following administration of LINZESS 290 mcg once daily for 7 days both in the non-fed and fed state in healthy subjects.

Distribution

Given that linaclotide plasma concentrations following recommended oral doses are not measurable, linaclotide is not expected to be distributed to tissues to any clinically relevant extent.

Elimination

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 fed and fasted healthy subjects following administration of LINZESS 290 mcg once daily for seven days averaged about 5% (fasted) and about 3% (fed) and all of it as the active metabolite.

Specific Populations

Renal and Hepatic Impairment

Renal or hepatic impairment is not expected to affect the clearance of linaclotide or the active metabolite because linaclotide metabolism occurs within the gastrointestinal tract and plasma concentrations are not measurable in plasma following administration of the recommended dosage.

Drug Interaction Studies

No drug-drug interaction studies have been conducted with LINZESS. Systemic exposures of drug and active metabolite are negligible following oral administration.

Linaclotide does not interact with the cytochrome P450 enzyme system based on the results of *in vitro* studies. In addition, linaclotide does not interact with common efflux and uptake transporters (including the efflux transporter P-glycoprotein (P-gp)). Based on these *in vitro* data no drug drug interactions through modulation of CYP enzymes or common transporters are anticipated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 2-year carcinogenicity studies, linaclotide was not tumorigenic in rats at doses up to 3500 mcg/kg/day or in mice at doses up to 6000 mcg/kg/day. The maximum recommended human dose is approximately 5 mcg/kg/day based on a 60-kg bodyweight. Limited systemic exposure to linaclotide and its active metabolite was achieved at the tested dose levels in animals, whereas no detectable exposure occurred in humans. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

Mutagenesis

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.

Impairment of Fertility

Linaclotide had no effect on fertility or reproductive function in male and female rats at oral doses of up to 100,000 mcg/kg/day.

14 CLINICAL STUDIES

14.1 Irritable Bowel Syndrome with Constipation (IBS-C)

The efficacy of LINZESS for the management of symptoms 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 [overall mean age of 44 years (range 18 to 87 years), 90% female, 77% white, 19% black, and 12% Hispanic] received treatment with LINZESS 290 mcg or placebo once daily and were evaluated for efficacy. 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-to-10-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 laxatives, bismuth, prokinetic agents, or other drugs to treat IBS-C or chronic constipation.

Efficacy of LINZESS was assessed using overall responder analyses and change-from-baseline endpoints. Results for endpoints were based on information provided daily by patients in diaries.

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.

The efficacy results for the 9 out of 12 weeks and the 6 out of 12 weeks responder endpoints are shown in Tables 3 and 4, respectively. In both trials, the proportion of patients who were responders to LINZESS 290 mcg was statistically significantly higher than with placebo.

Table 3: Efficacy Responder Rates in the Two Placebo-controlled IBS-C Trials: at Least 9 Out of 12 Weeks

	Trial 1			Trial 2		
	LINZESS 290 mcg (N=405)	Placebo (N=395)	Treatment Difference [95% CI]	LINZESS 290 mcg (N=401)	Placebo (N=403)	Treatment Difference [95% CI]
Combined Responder* (Abdominal Pain and CSBM Responder)	12%	5%	7% [3.2%, 10.9%]	13%	3%	10% [6.1%, 13.4%]
Abdominal Pain Responder* (≥ 30% Abdominal Pain Reduction)	34%	27%	7% [0.9%, 13.6%]	39%	20%	19% [13.2%, 25.4%]
CSBM Responder* (≥ 3 CSBMs and Increase ≥1 CSBM from Baseline)	20%	6%	13% [8.6%, 17.7%]	18%	5%	13% [8.7%, 17.3%]
* Primary Endpoints Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2 CI =Confidence Interval						

Table 4: Efficacy Responder Rates in the Two Placebo-controlled IBS-C Trials: at Least 6 Out of 12 Weeks

	Trial 1			Trial 2		
	LINZESS 290 mcg (N=405)	Placebo (N=395)	Treatment Difference [95% CI]	LINZESS 290 mcg (N=401)	Placebo (N=403)	Treatment Difference [95% CI]
Combined Responder* (Abdominal Pain and CSBM Responder)	34%	21%	13% [6.5%, 18.7%]	34%	14%	20% [14.0%, 25.5%]
Abdominal Pain Responder** (≥ 30% Abdominal Pain Reduction)	50%	37%	13% [5.8%, 19.5%]	49%	34%	14% [7.6%, 21.1%]
CSBM Responder** (Increase ≥ 1 CSBM from Baseline)	49%	30%	19% [12.4%, 25.7%]	48%	23%	25% [18.7%, 31.4%]
* Primary Endpoint, ** Secondary Endpoints Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2 CI =Confidence Interval						

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, LINZESS 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). Maximum effect on CSBM frequency occurred within the first week, and for change from baseline in CSBM frequency at week 12, the difference between placebo and LINZESS was approximately 1.5 CSBMs per week in both trials.

In each trial, in addition to improvements in abdominal pain and CSBM frequency over the first 12 weeks of the treatment period, improvements were observed in the following when LINZESS was compared to placebo: SBM frequency [SBMs/week], stool consistency [as measured by the Bristol Stool Form Scale (BSFS)], and amount of straining with bowel movements [amount of time pushing or physical effort to pass stool].

During the 4-week randomized withdrawal period in Trial 1, patients who received LINZESS during the 12-week treatment period were re-randomized to receive placebo or continue

treatment on LINZESS 290 mcg. In LINZESS-treated patients re-randomized to placebo, CSBM frequency and abdominal-pain severity returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on LINZESS maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to LINZESS had an increase in CSBM frequency and a decrease in abdominal pain levels that were similar to the levels observed in patients taking LINZESS during the treatment period.

14.2 Chronic Idiopathic Constipation (CIC)

The efficacy of LINZESS for the management of symptoms of CIC was established in two double-blind, placebo-controlled, randomized, multicenter clinical trials in adult patients (Trials 3 and 4). A total of 642 patients in Trial 3 and 630 patients in Trial 4 [overall mean age of 48 years (range 18 to 85 years), 89% female, 76% white, 22% black, 10% Hispanic] received treatment with LINZESS 145 mcg, 290 mcg, or placebo once daily and were evaluated for efficacy. All patients met modified Rome II criteria 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:

- 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 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 laxatives, bismuth, prokinetic agents, or other drugs to treat chronic constipation.

The efficacy of LINZESS was assessed using a responder analysis and change-from-baseline endpoints. Results for endpoints were based on information provided daily by patients in diaries.

A CSBM responder in the CIC trials was defined as a patient 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. The CSBM responder rates are shown in Table 5. During the individual double-blind placebo-controlled trials, LINZESS 290 mcg did not consistently offer additional clinically meaningful treatment benefit over placebo than that observed with the LINZESS 145 mcg dose. Therefore, the 145 mcg dose is the recommended dose. Only the data for the approved 145 mcg dose of LINZESS are presented in Table 5.

In Trials 3 and 4, the proportion of patients who were CSBM responders was statistically significantly greater with the LINZESS 145 mcg dose than with placebo.

Table 5: Efficacy Responder Rates in the Two Placebo-controlled CIC Trials: at Least 9 Out of 12 Weeks

	Trial 3			Trial 4		
	LINZESS 145 mcg (N=217)	Placebo (N=209)	Treatment Difference [95% CI]	LINZESS 145 mcg (N=213)	Placebo (N=215)	Treatment Difference [95% CI]
CSBM Responder* (≥ 3 CSBMs and Increase ≥ 1 CSBM from Baseline)	20%	3%	17% [11.0%, 22.8%]	15%	6%	10% [4.2%, 15.7%]
*Primary Endpoint CI=Confidence Interval						

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 LINZESS was approximately 1.5 CSBMs.

On average, patients who received LINZESS across the 2 trials had significantly greater improvements compared with patients receiving placebo in stool frequency (CSBMs/week and SBMs/week), and stool consistency (as measured by the BSFS).

In each trial, in addition to improvements in CSBM frequency over the first 12 weeks of the treatment period, improvements were observed in each of the following when LINZESS was compared to placebo: SBM frequency [SBMs/week], stool consistency [as measured by the BSFS], and amount of straining with bowel movements [amount of time pushing or physical effort to pass stool].

During the 4-week randomized withdrawal period in Trial 3, patients who received LINZESS during the 12-week treatment period were re-randomized to receive placebo or continue treatment on the same dose of LINZESS taken during the treatment period. In LINZESS-treated patients re-randomized to placebo, CSBM and SBM frequency returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on LINZESS maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to LINZESS had an increase in CSBM and SBM frequency similar to the levels observed in patients taking LINZESS during the treatment period.

A 72 mcg dose of LINZESS was established in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients (Trial 5). A total of 1223 patients [overall mean age of 46 years (range 18 to 90 years), 77% female, 71% white, 24% black, 43%

Hispanic] received treatment with LINZESS 72 mcg or placebo once daily and were evaluated for efficacy. All patients met modified Rome III criteria for functional constipation. Trial 5 was identical to Trials 3 and 4 through the first 12 weeks. The efficacy of the 72 mcg dose was assessed using a responder analysis where a CSBM responder was defined as a patient 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, which was the same as the one defined in Trials 3 and 4. The response rates for the CSBM responder endpoint were 13% for LINZESS 72 mcg and 5% for placebo. The difference between LINZESS 72 mcg and placebo was 9% (95% CI: 4.8%, 12.5%).

A separate analysis was performed using an alternate CSBM responder definition. In this analysis a CSBM responder was defined as a patient 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 and at least 3 of the last 4 weeks of the treatment period. The response rates for the alternate CSBM responder endpoint were 12% for LINZESS 72 mcg and 5% for placebo. The difference between LINZESS 72 mcg and placebo was 8% (95% CI: 3.9%, 11.5%).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LINZESS Capsule Strength	Description	Packaging	NDC number
72 mcg	White to off-white opaque hard gelatin capsules with gray imprint "FL 72"	Bottle of 30	0456-1203-30
145 mcg	White to off-white opaque hard gelatin capsules with gray imprint "FL 145"	Bottle of 30	0456-1201-30
290 mcg	White to off-white opaque hard gelatin capsules with gray imprint "FL 290"	Bottle of 30	0456-1202-30

Storage

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Keep LINZESS 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients:

Diarrhea

- To stop LINZESS and contact their healthcare provider if they experience unusual or severe abdominal pain, and/or severe diarrhea, especially if in combination with hematochezia or melena [see *Warnings and Precautions (5.2)*].

Accidental Ingestion

- Accidental ingestion of LINZESS in children especially in children less than 6 years of age may result in severe diarrhea and dehydration. Instruct patients to take steps to store LINZESS securely and out of reach of children, and to dispose of unused LINZESS [see *Contraindications (4)*, *Warnings and Precautions (5.1, 5.2)*].

Administration and Handling Instructions

- To take LINZESS once daily on an empty stomach at least 30 minutes prior to the first meal of the day [see *Dosage and Administration (2.2)*].
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take 2 doses at the same time.
- To swallow LINZESS capsules whole. Do not crush or chew capsules or capsule contents.
- If adult patients have swallowing difficulties, LINZESS capsules can be opened and administered orally in either applesauce or with bottled water or administered with water via a nasogastric or gastrostomy tube, as described in the Medication Guide.
- To keep LINZESS in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles closed tightly in a dry place.

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Allergan USA, Inc.
Irvine, CA 92612

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Irvine, CA 92612 Cambridge, MA, 02142

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MEDICATION GUIDE
LINZESS® (lin-ZESS)
(linaclotide)
capsules, for oral use

What is the most important information I should know about LINZESS?

- Do not give LINZESS to children who are less than 6 years of age. It may harm them.
- You should not give LINZESS to children 6 to 17 years of age. It may harm them.

See the section "**What are the possible side effects of LINZESS?**" for more information about side effects.

What is LINZESS?

LINZESS is a prescription medicine used in adults to treat:

- irritable bowel syndrome with constipation (IBS-C).
- a type of constipation called chronic idiopathic constipation (CIC). "Idiopathic" means the cause of the constipation is unknown.

It is not known if LINZESS is safe and effective in children less than 18 years of age.

Who should not take LINZESS?

- **Do not give LINZESS to children who are less than 6 years of age.** LINZESS can cause severe diarrhea and your child could get severe dehydration (loss of a large amount of body water and salt).
- Do not take LINZESS if a doctor has told you that you have a bowel blockage (intestinal obstruction).

Before you take LINZESS, tell your doctor about your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if LINZESS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LINZESS passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take LINZESS.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

How should I take LINZESS?

- Take LINZESS exactly as your doctor tells you to take it.
- Take LINZESS 1 time each day on an empty stomach, at least 30 minutes before your first meal of the day. You should also wait 30 minutes before eating a meal if you take LINZESS with applesauce or mixed with water.
- If you miss a dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time.
- LINZESS capsules should be swallowed whole. Do not crush or chew LINZESS.
 - Adults who cannot swallow LINZESS capsules whole may open the LINZESS capsule and sprinkle the LINZESS beads over applesauce or mix LINZESS with bottled water before swallowing.

It is not known if LINZESS is safe and effective when sprinkled on other foods or mixed with other liquids.

Taking LINZESS in applesauce:

- Place 1 teaspoon of room temperature applesauce into a clean container. Open the LINZESS capsule and sprinkle all of the LINZESS beads onto the applesauce.
- Swallow all of the LINZESS beads and applesauce right away. Do not keep the applesauce for later use.
- Do not chew the LINZESS beads.

Taking LINZESS in water:

- Pour 1 ounce (30 mL) of room temperature bottled water into a clean cup. Open the LINZESS capsule and sprinkle all of the LINZESS beads into the cup of water.
- Gently swirl the beads and water for at least 20 seconds.
- Swallow all of the LINZESS beads and water mixture right away. Do not keep the mixture for later use.
- If you see any LINZESS beads left in the cup, add another 1 ounce (30mL) of water to the beads in the cup, swirl for at least 20 seconds, and swallow right away.

Taking LINZESS in a nasogastric or gastrostomy feeding tube:

Gather the supplies you will need to take your LINZESS dose. Your doctor should tell you what size catheter tipped syringe you will need for your dose. Ask your doctor if you have any questions about how to give LINZESS the right way.

- Open the LINZESS capsule and pour all of the LINZESS beads into a clean container with 1 ounce (30 mL) of room temperature bottled water.
- Gently swirl the beads and water for at least 20 seconds.
- Remove the plunger from the catheter tipped syringe, and then pour the LINZESS bead and water mixture into the syringe and replace the plunger.
- Remove the cap from the syringe, insert the tip of the syringe into the nasogastric or gastric feeding tube and push the plunger all the way in to give the dose.
- If you see any LINZESS beads left in the container, add another 1 ounce (30 mL) of water to the beads in the container and repeat the process.
- After giving the LINZESS dose, flush the nasogastric or gastrostomy tube with at least 10 mL of water.

What are the possible side effects of LINZESS?

LINZESS can cause serious side effects, including:

- See “**What is the most important information I should know about LINZESS?**”
- **Diarrhea is the most common side effect of LINZESS, and it can sometimes be severe.**
 - Diarrhea often begins within the first 2 weeks of LINZESS treatment.
 - **Stop taking LINZESS and call your doctor right away if you get severe diarrhea during treatment with LINZESS.**

Other common side effects of LINZESS include:

- gas
- stomach-area (abdomen) pain
- swelling, or a feeling of fullness or pressure in your abdomen (distention)

Call your doctor or go to the nearest hospital emergency room right away, if you develop unusual or severe stomach-area (abdomen) pain, especially if you also have bright red, bloody stools or black stools that look like tar.

These are not all the possible side effects of LINZESS.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LINZESS?

- Store LINZESS at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep LINZESS in the bottle that it comes in.
- The LINZESS 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 bottle of LINZESS tightly closed and in a dry place.

Keep LINZESS and all medicines out of the reach of children.

General information about LINZESS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LINZESS for a condition for which it was not prescribed. Do not give LINZESS to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your doctor or pharmacist for information about LINZESS that is written for health professionals.

What are the ingredients in LINZESS?

Active ingredient: linaclotide

Inactive ingredients for the 145 mcg and 290 mcg capsules: calcium chloride dihydrate, hypromellose, L-leucine, and microcrystalline cellulose. Capsule shell: gelatin and titanium dioxide.

Inactive ingredients for the 72 mcg capsules: calcium chloride dihydrate, L-histidine, microcrystalline cellulose, polyvinyl alcohol, and talc. Capsule shell: gelatin and titanium dioxide.

LINZESS® is a registered trademark of Ironwood Pharmaceuticals, Inc.

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For more information, go to www.LINZESS.com or call 1-800-433-8871.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 01/2017

EEK KIT – LABEL

**LOT/EXP DATE
CODE AREA**

ID CODE

XXXXX

Rev. XX/XX/XXXX

Rx Only **30 CAPSULES**
Professional Sample–Not for Sale **NDC 0456-1203-31**

Linzess[®]
(linaclotide) capsules

72 mcg /capsule

ATTENTION PRESCRIBER:
**Each patient is required to receive
the enclosed Medication Guide.**

**Keep LINZESS in the original container
to protect from moisture. Do not remove
the desiccant from inside the bottle.**

KEEP OUT OF REACH OF CHILDREN.
Each capsule contains 72 mcg linaclotide

Store at 25°C (77°F); excursions permitted
between 15°C and 30°C (59°F and 86°F).

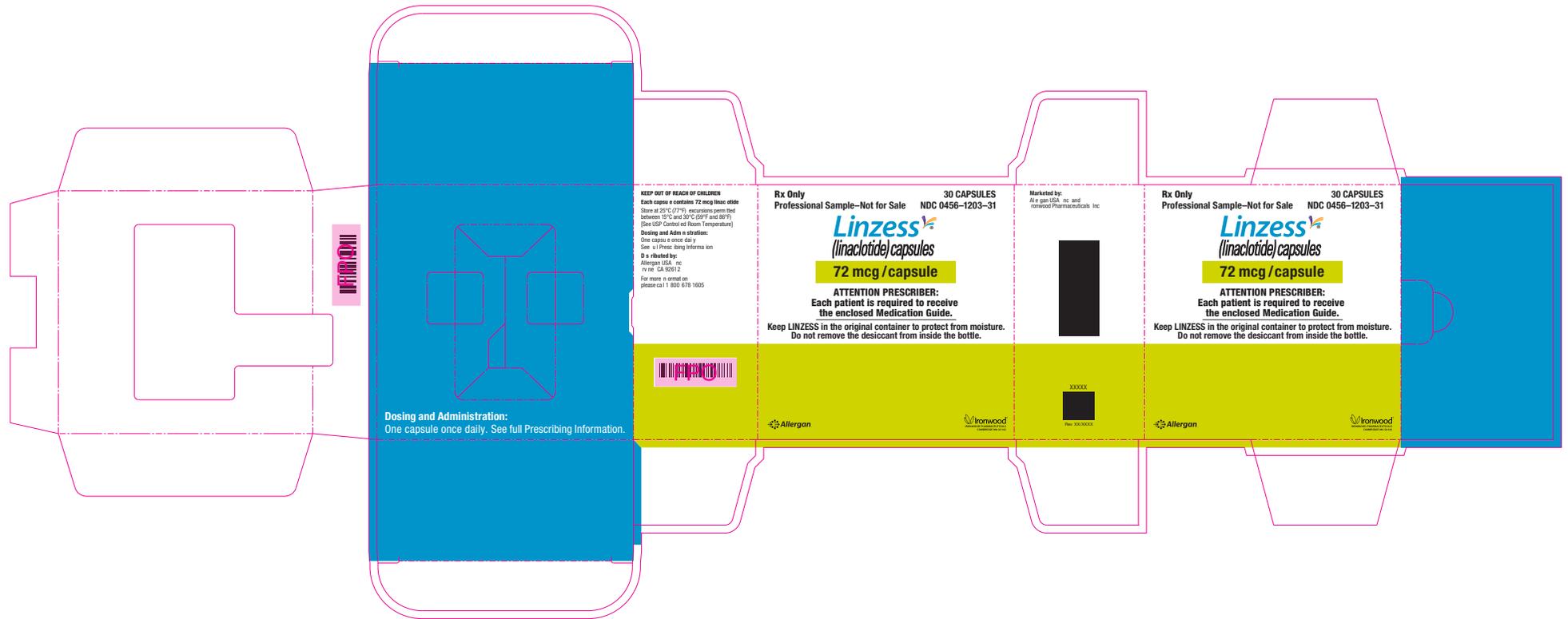
Dosing and Administration:
One capsule once daily.
See full Prescribing Information.

Distributed by:
Allergan USA, Inc.
Irvine, CA 92612

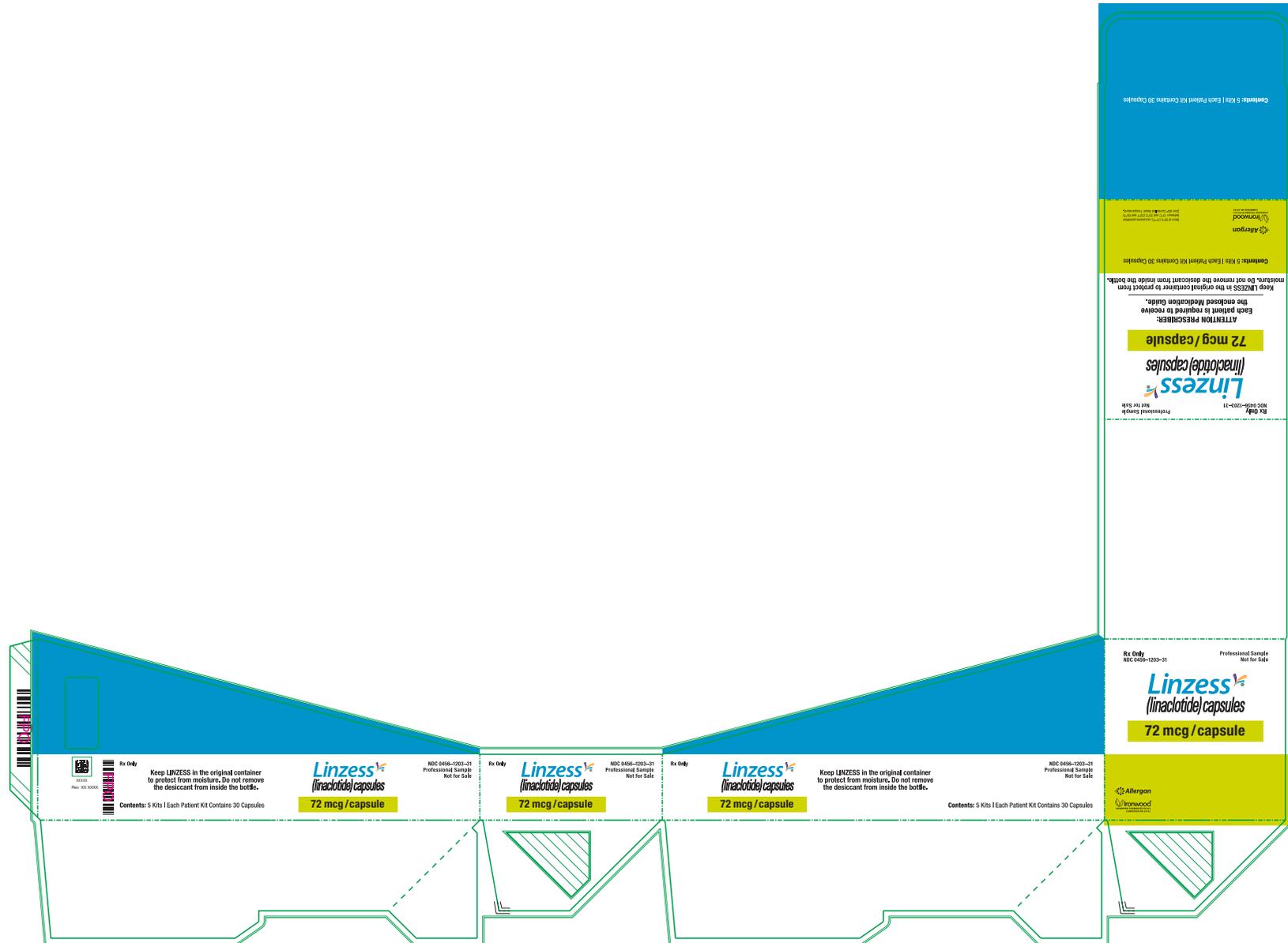
For more information,
please call 1-800-678-1605.

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Ironwood Pharmaceuticals, Inc.

EEK KIT – BOX



EEK KIT – TRAY



RETAIL PACKAGING – LABEL

Rx Only **NDC 0456-1203-30**

30 CAPSULES

Linzess[®]
(linaclotide) capsules

72 mcg / capsule

ATTENTION PHARMACIST:
Each patient is required to receive
the enclosed Medication Guide.

Keep LINZESS in the original container
to protect from moisture. Do not remove
the desiccant from inside the bottle.

KEEP OUT OF REACH OF CHILDREN.

Each capsule contains 72 mcg
linaclotide

Store at 25°C (77°F); excursions permitted
between 15°C and 30°C (59°F and 86°F).

Dosing and Administration:
One capsule once daily.
See full Prescribing Information.

Distributed by:
Allergan USA, Inc.
Irvine, CA 92612

For more information,
please call 1-800-678-1605.

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Irvine, CA 92612
Ironwood Pharmaceuticals, Inc.
Cambridge, MA, 02142
XXXXX XX/XXXX

SAMPLE PACKAGING – LABEL

Rx Only **4 CAPSULES**
Professional Sample–Not for Sale

Linzess
(linaclotide) capsules

72 mcg / capsule

ATTENTION PRESCRIBER:
Each patient is required to receive the enclosed Medication Guide.
Keep LINZESS in the original container to protect from moisture. Do not remove the desiccant from inside the bottle.

NDC 0456-1203-04
KEEP OUT OF REACH OF CHILDREN.
Each capsule contains 72 mcg linaclotide
Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).
Dosing and Administration:
One capsule once daily. See full Prescribing Information.
Distributed by:
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XXXXX
ID CODE
Rev. XX/XXXX

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CODE AREA

SAMPLE PACKAGING – BOX



EK KIT – SLEEVE



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/s/

JOYCE A KORVICK
01/25/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, M.D., M.P.H.
Subject	Division Signatory Summary Review
NDA #	202811
Supplement #	s-010
Applicant Name	Forest Laboratories and Ironwood Pharmaceuticals
Date of Submission	3/25/2016
PDUFA Goal Date	1/25/2017
Proprietary Name / Established (USAN) Name	Linzess (linaclotide) capsules, for oral use
Dosage Forms / Strength	Capsule, 72 mcg
Proposed Indication(s)	Chronic Idiopathic Constipation (new dose)
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Preeti Venkataraman
Statistical Review	Shahla Farr
OPQ Review	Hossein Khorshidi, Kelly Kitchens
Clinical Pharmacology Review	Sandhya Apparaju
Pharmacometrics	Jee Dun Lee
OPDP	Meeta Patel
OSI	Susan Liebenhaut
DPMH	Jane Liedtka, Ethan Hausman
DMPP	Nyedra Booker
OSE/DMEPA	Sherly Abraham
OSE/DPV	Lisa Harinstein
Division Director Review (2012)	Donna Griebel

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 DMPP= Division of Medical Policy Programs.
 DPV= Division of Pharmacovigilance
 OPDP= Office of Prescription Drug Promotion
 OPQ= Office of Pharmaceutical Quality
 DPMH= Division of Pediatric and Maternal Health

1. Introduction

This supplemental NDA proposes a new dosing regimen for the treatment of chronic idiopathic constipation (CIC) in adults. The sponsor proposes the use of a single 72 mcg dose of linaclotide (Linzess). Linaclotide is currently approved for CIC in adults with the recommended daily dose of 145 mcg. The Applicant proposes the new dose to be both effective for the treatment of CIC and have a lower amount of abdominal side effects, potentially making it more tolerable for some patients considering the higher approved dose. Linaclotide is an endogenous guanylin peptide that serves as a Guanylate cyclase-C (GC-C) receptor agonist, and exerts its action locally in the GI tract to provide relief from constipation in patients with CIC.

Linaclotide is structurally related to human guanylin and uroguanylin and functions as a guanylate cyclase-C (GC-C) agonist. 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, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, linaclotide has been shown to both accelerate GI transit and reduce intestinal pain. In an animal model of visceral pain, linaclotide reduced abdominal muscle contraction and decreased the activity of pain-sensing nerves by increasing extracellular cGMP.

This supplemental application relies on data from one phase 3 double blind, randomized, placebo controlled trial comparing linaclotide 72 mcg and 145 mcg to placebo, as well as findings from a previously reviewed phase 2 dose comparison study evaluated during the original application cycle.

2. Background

Linaclotide was approved on August 30, 2012 for the treatment of irritable bowel disease-with constipation (IBS-C) at a daily dose of 290 mcg, and CIC at a daily dose of 145 mcg. There are four prescription drug products approved for the treatment of CIC: linaclotide (Linzess), lubiprostone (Amitiza), tegaserod maleate (Zelnorm [no longer marketed – available through expanded access]), and most recently a second locally acting GC-C agonist plecanatide (Trulance). Lactulose is approved for the treatment of constipation. Over-the-counter products for the treatment of constipation include hyperosmotic laxatives, bulk-forming laxatives, stimulant laxatives, saline laxatives lubricant laxatives/stool softeners and enemas.

OIC is defined as a symptom-based disorder occurring over a chronic time course and characterized by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool. Patients with CIC also typically suffer from abdominal symptoms of varying severity, with no identifiable underlying cause (i.e., opioid use, mechanical obstruction, etc.). This disorder is one of the

most common functional gastrointestinal disorders worldwide, with a prevalence of approximately 14%.

In the original approval the efficacy of linaclotide for the treatment of CIC was demonstrated in two double blind, randomized, placebo controlled trials. The proportion of patients who were complete spontaneous bowel movement (CSBM) Responders was statistically significantly greater with the Linzess 145 mcg dose than with placebo (CSBM Responder rate was 20% and 15 %, with a treatment difference between Linzess and placebo of from 17% to 10%). The currently approved efficacy data for Linzess 145 mcg is described in the label. The reader is referred to the original approval for more detailed information found in the Division Director review (Donna Griebel, 8/29/2012).

In this supplement the Applicant provided a rationale for the use of the lower dose regimen. They note that patients with CIC suffer from a range of bowel symptoms of varying severities, may require individualized approaches to the management of their symptoms, may differ in their responsiveness to treatment with linaclotide in clinical practice, and that practicing physicians have suggested that the availability of a lower dose of linaclotide may be helpful in the clinical care of some CIC patients. Therefore, the Applicant has studied the safety and efficacy of linaclotide 72 mcg and is seeking approval of this dose.

The safety profile of the 72 mcg linaclotide dose is similar to that of the approved doses (See Safety section below).

As noted in the original Division Director review (2012) two safety issues remain a concern; pediatric safety and the theoretical potential for guanylin cyclase deficiency syndrome to develop. The potential for serious dehydration which may lead to death resulted in the current Boxed Warning. Linzess is contraindicated in “pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age”. Since the approval of this drug product we have opened a TSI 1737 [REDACTED] (b) (4). This will be discussed in the safety section below.

3. OPQ

Biopharmaceutics reviewer concluded: “The Applicant will apply the approved dissolution method for Linzess® (linaclotide) Capsules for the quality control testing at release and stability of the proposed 72 mcg strength. The proposed dissolution acceptance criterion, $Q = \frac{(b)}{(4)}\%$ in 15 minutes, is adequate based on the dissolution data submitted. From the Biopharmaceutics perspective, NDA 202811/S-010 for Linzess® (linaclotide) Capsules is recommended for approval.”

Chemistry, Manufacturing and Controls:

The primary objective of this supplement was to introduce a new strength (72 mcg) of Linaclotide. The drug substance is the same as that of the already marketed drug. This product used the same manufacturing facilities as the currently approved drug products. There

we three excipients that were different from the currently marketed products. These were found acceptable.

The categorical exclusion form Environmental Assessment was acceptable to the reviewers. The chemistry reviewers recommended approval of the 72mcg capsule.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical studies submitted to this application. The reviewers worked with the team to update the labeling regarding the pediatric and maternal health sections of the labeling. The final approved labeling contains those recommendations.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Pharmacometrics

The Clinical Pharmacology reviewer states:

“There was no new Clinical Pharmacology information in this sNDA. The supporting dose-ranging study MCP-103-201 was reviewed during the original approval cycle by OCP. Please refer to Clinical Pharmacology review dated 04/06/2012 in DARRTs for additional information on this dose-ranging trial”.

The Division of Pharmacometrics in OCP has looked into available dose-response information on request from clinical reviewers. They concluded that:

“Overall, it appears that there is no meaningful effect of baseline spontaneous bowel movement (SBM) rate (>1 SBM/week and ≤ 1 SBM/week) on dose-response relationship of linaclotide in study 309. However, cross study trial comparison of 201 (baseline SBM rate=2.22 /week) and 309 (baseline SBM rate 1.65 /week) did show a different dose response relationship. It is possible that this difference is due to different treatment duration or other baseline characteristics of the treated population. Nevertheless, based on the standalone Phase 3 study (Study 309), the proposed dose of 72 mcg QD appears to have similar effect compared to 145 mcg for the treatment of patients with CIC. This effect is consistent for both less and more symptomatic treatment population with both doses demonstrating treatment effect. Therefore, the results of study 309 support the approval 72 mcg QD for CIC.” Please refer to DARRTs for a separate review in this regard by Drs. Jee Eun Lee and Nitin Mehrotra.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

Two studies were submitted in support of the efficacy and safety of linaclotide 72 mcg daily for the treatment of CIC in adults:

- Study MCP-103-309- A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide (72 mcg or 145 mcg) Administered Orally for 12 Weeks to Patients with Chronic Idiopathic Constipation,
- Study MCP-103-201- A Randomized, Multicenter, Double-blind, Placebo-controlled, Dose-range-finding, Parallel-group, Phase 2 Trial of Oral Linaclotide Acetate Administered to Patients with Chronic Idiopathic Constipation.

Study MCP-103-309 was the pivotal study for this application. Subjects had to meet the modified Rome III criteria for diagnosis of CIC:

- < 3 SBMs per week and reported 1 or more of the following symptoms during the 3 months before the diagnosis with the onset at least 6 months before the diagnosis:
 - straining during $\geq 25\%$ of BMs
 - lumpy or hard stools during $\geq 25\%$ of BMs, and
 - a sensation of incomplete evacuation during $\geq 25\%$ of BMs.

The study design was very similar to the phase 3 studies in the original application for CIC. Dose selection was based on clinical results from the Phase 2 dose-range-finding trial (MCP-103-201), which evaluated daily linaclotide doses of 72, 145, 290, and 579 mcg versus placebo. In this study, linaclotide 72 mcg was reported to demonstrate efficacy over placebo and also had a lower incidence of diarrhea than linaclotide 145 mcg; thus linaclotide 72 mcg was chosen for evaluation in the MCP-103-309 trial. The approved dose of 145mcg was included as a positive control.

The primary endpoint in Study MCP-103-309 was a 12-week Complete Spontaneous Bowel Movement (CSBM) Overall Responder defined as follows:

- A 12-week CSBM Overall Responder was a patient who was a CSBM Weekly Responder for at least 9 of the 12 weeks of the Treatment Period.
 - A CSBM Weekly Responder for a Treatment Period week was a patient who had a CSBM weekly frequency rate that was 3 or greater and increased by 1 or more from baseline based on a minimum of 4 complete IVRS calls for that week. If a patient did not have at least 4 complete IVRS calls for a particular Treatment Period week, the patient was not considered a CSBM Weekly Responder for that week.*
- A 12-week CSBM Overall Sustained Responder was a patient who met the 12-week CSBM Overall Responder criteria as defined above, and additionally was a CSBM weekly responder for ≥ 3 of the last 4 weeks of the Treatment Period.

The clinical reviewer commented that “The above responder definitions are consistent with what DGIEP finds acceptable for CIC. However, durability of response (12-week CSBM Overall Sustained Responder) was evaluated as an additional efficacy parameter in a pre-specified sensitivity analysis, rather than as part of the primary endpoint as recommended by FDA.”

A 12-week CSBM Sustained Responder was assessed as a pre-specified sensitivity analysis of the primary endpoint, and was defined as a patient who was a CSBM Weekly Responder for at least 9 of the 12 weeks and at least 3 of the last 4 weeks of the Treatment Period.

The pre-specified primary efficacy parameter was 12-week CSBM Overall Responder which required patients to be weekly responders for at least 9 of 12 weeks. The proportion of CSBM Overall Responders over weeks 1 – 12 was significantly higher in patients receiving linaclotide 72mcg compared to placebo (13.4% vs 4.7%, $p < 0.0001$). The results of control group, linaclotide 145 mcg, compared to placebo were statistically significant (12.4% vs 4.7%, $p = 0.0001$). Although it is unclear what contributed to the difference between effect sizes between MCP-103-309 and the pivotal studies supporting the approval of the 145mcg dose, it appears that the 72mcg dose was demonstrated to be effective by achieving its primary endpoint. The primary reviewer concluded that this is a clinically meaningful outcome when the potential side effect profile may be improved (see safety section).

The sustainability of the 12-week CSBM Overall response was evaluated in a pre-specified sensitivity analysis and required patients to be weekly responders for at least 9 of the 12 weeks, including at least 3 of the last 4. The proportion of CSBM Sustained Responders over weeks 1-12 was significantly higher in patients receiving linaclotide 72mcg compared to placebo (12.4% vs 4.7%, $p = 0.0001$). The results in the 145 mcg treatment group compared to placebo were statistically significant (11.2% vs 4.7%, $p = 0.0010$).

Secondary endpoints are supportive of the overall effect of this lower dose. (see review by Dr. Venkataraman for further details). Linaclotide 72 mcg and 145 mcg demonstrated similar efficacy for CSBM 75% Responder, SBM and CSBM frequency rates, stool consistency, and straining.

The results from Study MCP-103-201 were relied upon as further evidence of efficacy of the 72 mcg dose. In MCP-103-201, the efficacy results appeared to demonstrate some efficacy of the 72mcg dose when compared to placebo, with comparability to the 145mcg dose. The change from baseline and response rates in the 72 mcg group were comparable to the 145mcg, with the exception of the CSBM 75% responder parameter. CSBM 75% responder rates were 7.4% for placebo, 18.6 % for 72 mcg and 26.8% for 145 mcg linaclotide.

Overall, this data demonstrates the efficacy of linaclotide 72 mcg dose compared to placebo. The use of the control group in the pivotal study suggests similar efficacy to the approved dose, however, this study was not powered to test that hypothesis. Data from the dose comparison study also support the efficacy findings of the single pivotal study.

The primary reviewer concluded that; “as the Applicant is seeking approval for a new dose strength in an indication for which linaclotide is already approved, this reviewer believes it is appropriate to rely, in part, on pertinent information from other adequate and well-controlled studies of other doses strengths for this indication, to support a single adequate and well-controlled study demonstrating effectiveness. The findings from MCP-103-309 are supported by MCP-103-201, and the 2 phase 3 trials conducted for original approval demonstrated efficacy of linaclotide at a higher dose for the same indication. This reviewer believes that the rationale provided above make it possible to rely on MCP-103-309 as a single adequate and well controlled study to provide sufficient scientific and legal basis for approval”.

I agree with the reviewer’s conclusion regarding efficacy of this new dose.

8. Safety

Overall the safety profile for the linaclotide 72 mcg dose appears similar to the already approved doses. Two safety issues of interest to this supplement are the rate of diarrhea, the most common abdominal side effect, and the potential for the development of the guanylin cyclase deficiency syndrome.

The Applicant has explored rates of the gastrointestinal side effects in Study MCP-103-309. There were no deaths in this study, and few serious adverse events. There were more patients who discontinued the study due to adverse events in the higher dose compared to linaclotide 27 mcg, and both rates were higher than placebo (2.9 %, 4.6%, 0.5%; 72 mcg, 145 mcg, placebo, respectively). Diarrhea was the most common adverse event leading to premature discontinuation among linaclotide patients, with 10 patients (2.4%) in the linaclotide 72 mcg group and 13 patients (3.2%) in the linaclotide 145 mcg group. Severe diarrhea treatment related adverse events were more frequent in the higher dose (2.4%, 0.5%, 0.7%; linaclotide 145 mcg, 72 mcg, placebo respectively). There appears to be a relationship of these events to the dosing.

As was noted in the original review of this NDA, due to the structural homology of endogenous guanylin peptide family members, concerns were raised that if anti-linaclotide antibodies were to develop, cross reaction with endogenous peptides could lead to deficiency syndromes. Potential clinical manifestations of loss of guanylin peptide function could include hypernatremia, volume overload, peripheral and pulmonary edema, fluid retention, weight gain, hypertension, hypernatremia, extremity swelling (excluding solitary joint swelling), and exocrine pancreatic insufficiency.

The medical reviewer searched the safety population submitted in this application. Of the terms that were searched for in the safety population [peripheral edema, fluid retention, pulmonary edema, hypertension (blood pressure increased), hypernatremia (sodium increased), weight increased, pancreatitis, lipase increased, extremity swelling, joint swelling], 4 patients were identified in the placebo arm (increased weight gain – 2 patients, hypertension – 1 patient, increased blood pressure – 1 patient), no patients were identified in the 72mcg dose arm, and 2 patients were identified in the 145mcg arm (hypernatremia – 1 patient, joint effusion – 1 patient). The reviewer went on to state that “The single patient with hypernatremia did not have any other symptoms indicative of guanylin deficiency, and had an

isolated elevated sodium of 150 that returned to normal at 142. Blood pressure was within normal limits and the subject completed the study. The event of joint effusion was associated with a fall and unlikely to be a sign of volume overload/fluid retention. In this reviewer's opinion, no evidence of a signal for a clinical deficiency syndrome was identified in the clinical safety dataset submitted with this sNDA." The Applicant also provided a supplement analysis of weight gain which did not reveal significant differences between placebo and treatment groups.

In order to broaden the search, the term weigh gain was used by the Division of Pharmacovigilance to review the post market database. When they limited the search to clinically significant weight gain there were only three cases that may be related to linaclotide, but two of them have limited data upon which to judge the relationship, and are confounded. While the reviews from DPV suggest adding weight gain to the label based on these cases, in further discussion with the Applicant and team during the final label negotiation, and based on the entire database reviewed and also the significant number of patients who have received this drug post marketing, and the propensity for weight gain in this population of middle aged women, it was decided that weight gain not be added to the label at this time. The current recommendation is that FDA continue routine post-market pharmacovigilance regarding this event.

I agree that there is a numerically lower event rate for the 72 mcg linaclotide dose for abdominal adverse events, particularly diarrhea. Also, at this time we have no evidence to support the potential for guanylin cyclase deficiency beyond what was stated in the original NDA review. (b) (4)

9. Advisory Committee Meeting

This NDA supplement was not referred to and Advisory Committee as there were no controversial issues associated with this lower dosage for an approved indication.

10. Pediatrics

PREA applies due to the approval of a new dosing regimen.

It is felt that CIC in adults may be different in pediatric patients, therefore in the original approval of CIC (date) for adults pediatric PREA studies were required.

PERC meeting on October 19, 2016 concluded: The PeRC agrees with the partial waiver request in pediatric patients birth to less than 2 years of age for safety and to deferral in patients 2 to 17 yrs.

Current PREA PMRS for CIC are as follows:

2161-2 Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 2 to 5 years treated with Linzess (linaclotide).

Final Protocol Submission	01/18
Study Completion	12/22

Final Report Submission 12/23

2161-3 Conduct a safety and efficacy study in pediatric patients with chronic Idiopathic constipation ages 6 to 17 years treated with Linzess (linaclotide).

Final Protocol Submission 04/15
Study Completion 12/22
Final Report Submission 12/23

The Applicant will be notified that these PREA PMRs apply to this supplemental approval as well. No new Pediatric studies are recommended. This was agreed upon with the PERC.

Current in-use labeling for Linzess, approved on August 31, 2016, is in the Physician Labeling Rule (PLR) format but does not comply with Pregnancy and Lactation Labeling Rule PLLR (requirements). The sponsor submitted the appropriate information for review based in response to a request by DGIEP. Those sections of the label were updated to comply with the PLLR requirements. There is a Boxed Warning and a Contraindication for use in pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of Linzess in pediatric patients 6 through 17 years of age.

The Maternal Health reviewer concluded that “The limited postmarketing experience with linaclotide in pregnancy is insufficient to establish the presence or absence of drug-associated risk. However, the lack of absorption suggests the risk to the fetus is minimal.” In addition, “There are no relevant new data regarding linaclotide use in lactating women. DPMH will revise the lactation section 8.2 to be consistent with the PLLR format and will continue to include the information that linaclotide is negligibly absorbed systemically following oral administration.”

Finally, based upon their review they stated “Since there are no human data available on the effect of linaclotide on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in linaclotide labeling.”

Appropriate changes were made to Pregnancy, Section 8.1 and Lactation, Section 8.2 of the labeling. See final approved label for details.

The pediatrics reviewer focused on Pediatric-related changes to labeling are restricted to moving the description of juvenile toxicity from section 13.2 (Animal Toxicology and/or Pharmacology) to section 8.4 of labeling and alternative “best word choices” pediatric language in the boxed warning and section 5 (Warnings and Precautions). The reviewer was involved in the final labeling negotiations. See approved final label for complete wording of this section.

Finally, considerations regarding including the description of animal testing and the inclusion of “human age equivalents” in the label were discussed. It was determined that based on the actual animal studies conducted, particularly the animals that died, the term “neonatal (human age equivalent of approximately 0 to 28 days)” would be included where these results were

discussed. In calculating these ages the non-clinical pharmacology toxicology review used the following reference: Barrow PC, page 413: in: Nonclinical Drug Safety Assessment: Practical Considerations for Successful Registration Editors: Sietsema WK & Schwen RS. 2007. The DPMH review team agreed to the use of this in section 8.4 of the physician labeling. Other than the use of the terminology “neonatal” no other age equivalent statements were made in section 8.4 based on the recommendation from the DPMH review team. They stated that including additional age equivalents in this section would be confusing to the reader, and that the clinical trials are under way in older pediatric patients. This section will be revised in the future based upon results of the pediatric studies.

I have reviewed the final labeling and am in agreement with these recommendations which bring this labeling into compliance with PLLR requirements.

11. Other Relevant Regulatory Issues

- OSI Audits: there were no issues regarding the conduct of the clinical trials, therefore, no site inspections were conducted.
- Financial Disclosure: acceptable.

There are no other unresolved relevant regulatory issues

12. Labeling

Includes:

- Proprietary name: there were no changes made to the name, additional dosage was added.
- Physician labeling
 - Section 14: improvements in the CIC section regarding the description of efficacy were made. It is important to avoid jargon and terminology which may lead to confusion, but rather to be descriptive regarding trial results. To this end the Applicant has removed the term “Overall” ^{(b) (4)} used before the word Responder. The definition of a responder whether as part of a primary analysis or as a secondary analysis is currently in the label. The Applicant accepted these changes. New data regarding the 72 mcg linaclotide dose regimen was included.
 - The Boxed Warning was revised in order to more clearly state the risks related to age.
 - Animal age equivalents are added to the label, particularly in Section 8 of the prescription label. This was recommended to make the data more clinically relevant (see Section 10 above regarding details).
- Carton and immediate container labels:
DMEPA comments:
“Therefore, we find the addition of the 72 mcg strength and the proposed Prescribing Information acceptable from a medication error perspective. However, the proposed

carton labeling and container label can be improved to ensure adequate differentiation between the strengths.”

“We recommend the following be implemented prior to approval of this Supplement:

Revise the (b) (4) proprietary name (b) (4)
the 72 mcg strength (b) (4)

(b) (4)
This issue was
successfully resolved.

- **Patient Labeling/Medication Guide**
The Medication Guide was updated based upon recommendations by the Division of Medical Policy Programs. See final approved version for final wording.

OPDP review was considered in labeling negotiations.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** APPROVAL
- **Risk Benefit Assessment:** The efficacy of the 72 mcg dose of linaclotide was demonstrated in Study MCP-103-309, and supported by the dose response relationship in the phase 2 dose escalation study when compared to placebo. Further there was a smaller rate of patients exposed to linaclotide having severe diarrhea or withdrawing due to adverse events in this 72 mcg linaclotide dose compared to the 145 mcg linaclotide dose. CIC is a chronic and debilitating condition. Being able continue receiving the effect of linaclotide while lowering the amount of gastrointestinal side effects is an important benefit to patients. Given these considerations both the medical reviewer and I agree that the benefit-risk of this dose of linaclotide is favorable and that it should be approved for treatment of OIC in adults.
- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS):**

No REMS was recommended or necessary based on the Risk Benefit Assessment.

- **Recommendation for other Postmarketing Requirements and Commitments:**
No new safety signals were identified since approval of this drug therefore no new safety PMR or PMC were required. No new Pediatric PREA studies were required (see Pediatric section above for discussion of PREA PMRs).

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JOYCE A KORVICK
01/25/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

OFFICER/EMPLOYEE LIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 25, 2017

TO: File

THROUGH: **Brian Strongin, R.Ph., M.B.A., Chief, Project Management Staff**

FROM: CDR Cheronda Cherry-France, RN, BSN, MHA, Regulatory Project Manager

SUBJECT: **Office/Employee List**

APPLICATION/DRUG: **NDA 202811/S-010 Linzess (linaclotide) capsules**

The following officers or employees of the FDA participated in the decision to approve this application and consented to be identified on this list:

Muldowney, Laurie
Lee, Sue Chih
Joseph, David
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Mehrotra, Nitin
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CHERONDA L CHERRY-FRANCE
01/25/2017

BRIAN K STRONGIN
01/25/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type sNDA
Application Number(s) 202811 (s-010)
Priority or Standard S

Submit Date(s) 3/25/2016
Received Date(s) 3/25/2016
PDUFA Goal Date 1/27/2017
Division / Office DGIEP

Reviewer Name(s) Preeti Venkataraman
Review Completion Date 12/1/2016

Established Name linaclotide
(Proposed) Trade Name Linzess®
Therapeutic Class Laxative (Locally acting
Guanylate Cyclase C
receptor agonist)
Applicant Forest Laboratories

Formulation(s) Capsule
Dosing Regimen 72ug
Indication(s) Chronic Idiopathic
Constipation (CIC)
Intended Population(s) Adult patients with CIC

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of Linzess® (linaclotide) 72ug orally once a day for the treatment of Chronic Idiopathic Constipation (CIC) in adult patients based on the Sponsor's demonstration of an acceptable safety and efficacy profile. Approval of linaclotide 72ug orally once a day for the treatment of Chronic Idiopathic Constipation in adult patients is contingent upon the Sponsor incorporating the Agency's recommended changes to the linaclotide drug label.

1.2 Risk Benefit Assessment

Chronic Idiopathic Constipation (CIC), also referred to as functional constipation, is defined as a symptom-based disorder occurring over a chronic time course and characterized by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool. Patients with CIC also typically suffer from abdominal symptoms of varying severity, with no identifiable underlying cause (i.e., opioid use, mechanical obstruction, etc.). This disorder is one of the most common functional gastrointestinal disorders worldwide, with a prevalence of approximately 14%. The current treatment options for CIC include prescription therapies, including linaclotide (Linzess) 145ug, a variety of over-the-counter therapies (e.g., laxatives, stool softeners, enemas), dietary management, and behavioral therapy. However, these options are not completely effective for all patients with CIC, and may cause significant side effects such that patients may require individualized approaches to the management of their symptoms.

Since there are a limited number of approved therapies for CIC, additional treatment options are needed for those who may respond to prescription medications, but who experience intolerability at a particular or higher doses. Linaclotide is an endogenous guanylin peptide that serves as a Guanylate cyclase-C (GC-C) receptor agonist, and exerts its action locally in the GI tract to provide relief from constipation in patients with CIC. Linaclotide 145ug is currently approved in CIC.

This efficacy supplement demonstrates the efficacy and safety of linaclotide 72ug as a treatment for adults with CIC. The data from 1 phase 3 adequate and well-controlled study favored linaclotide 72ug for the primary efficacy endpoint of the proportion of overall complete spontaneous bowel movement (CSBM) responders during the 12-week treatment period. The Applicant's worst case analysis of the primary endpoint, which was the prespecified primary analysis, yields a treatment difference of 8.7% and a p-value of <0.0001. Although the treatment difference is somewhat lower than the

effect size demonstrated in the trials conducted to support the approval of Linzess in CIC (16.9% and 9.9%), a statistically significant difference in the primary endpoint may be considered clinically meaningful by the Division if it is accompanied by some reduction in risk and/or improvement in tolerability. The sustainability of the 12-week CSBM Overall response was evaluated in a pre-specified sensitivity analysis and the proportion of CSBM sustained responders was significantly higher in patients receiving linaclotide 72ug compared to placebo. The secondary endpoints were adjusted for multiplicity, and generally appear to be supportive of the primary endpoint results. Although the treatment difference between linaclotide 72ug and placebo is fairly moderate, the lower dosage strength of 72ug offers an alternative therapeutic option with an improved tolerability profile for patients who suffer from CIC and are unable to tolerate the higher 145ug dose. Data from a phase 2b trial evaluating the 72ug dose appear supportive of the primary endpoint results.

The analysis of safety show that linaclotide is safe and well tolerated at the 72ug dose in the treatment of patients with CIC. The most common AEs appear consistent with the known activity of linaclotide, and with that of the already approved 145ug dose. Compared with the approved dose of linaclotide 145 ug for the treatment of CIC, linaclotide 72 ug demonstrates lower diarrhea rates, less severe diarrhea, and fewer diarrhea adverse events leading to dropout. Safety results from both the pivotal phase 3 trial and the supportive phase 2b trial demonstrate that the 72ug dose has a better tolerability profile than the 145ug dose in terms of the most common side effect of linaclotide, diarrhea. It should be noted that several potential cases of ischemic colitis were identified in the clinical development program for linaclotide, at both the 145ug and 72ug doses. However, there is insufficient evidence at this time to confirm an association between linaclotide use and ischemic colitis. There also exists a hypothetical concern that due to the structural homology of linaclotide with endogenous guanylin peptide family members, development of anti-drug antibodies could cross react with endogenous guanylin peptides that could lead to deficiency syndromes. However, no evidence of a signal for a clinical deficiency syndrome (peripheral edema, fluid retention, pulmonary edema, hypertension, hypernatremia, weight increased, pancreatitis, lipase increased, extremity swelling, joint swelling) was identified in the clinical safety dataset submitted with this sNDA.

The pediatric population is currently under study in the linaclotide development program. At the time of original approval, neonatal/juvenile mice oral toxicity studies revealed that young mice were particularly sensitive to linaclotide toxicity, and a lethality signal was observed which was highly age-dependent. These nonclinical study findings, suggesting an age-dependency of the pharmacodynamic response, indicate that it is not safe to administer linaclotide to children < 2 years of age. A PMR to measure GC-C mRNA levels in duodenal and colonic tissue in children ages 0 to 6 years of age is currently ongoing to determine the potential risk of a significant fluid shift into the intestine. Results from this GC-C mRNA study as well as results from an ongoing CIC clinical trial of children ages 6-17 years of age will inform the trial design

for a phase 2 CIC study in children ages 2-5 years of age. Currently and until such time that this concern is addressed, there is a boxed warning in the labeling with a contraindication in pediatric patients up to 6 years, and use of linaclotide in pediatric patients 6 through 17 years of age is to be avoided. A PMR to determine the safety of linaclotide for breast-fed infants whose mothers are receiving therapy are ongoing. Lastly, PMRs to determine the immunogenic potential of linaclotide are pending.

The expansion of the indication for Linzess® 145ug orally once daily for adults with Chronic Idiopathic Constipation to include the dose of 72ug orally once daily in adults with Chronic Idiopathic Constipation provides patients with an alternative to a higher dose to treat the same condition. In this reviewer's assessment, the MCP-103-309 clinical trial of Linzess® 72ug orally QD demonstrates efficacy in subjects with CIC when compared with placebo. In light of the favorable safety profile and overall treatment effect of 8.7% over placebo, in this reviewer's assessment Linzess® can be an effective and safe option.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

After a thorough safety review and analysis, this clinical reviewer believes that a postmarketing risk evaluation and mitigation strategy is not needed for linaclotide.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no new recommendations for postmarket requirements or commitments. However, the postmarketing requirements (PMRs), including the Pediatric Research Equity Act (PREA) PMRs listed below, are associated with the original approval of this product and apply to this application:

FDAAA Safety PMRs:

- 1915-4: Develop and validate sensitive and precise assays for the detection of anti-linaclotide antibodies, including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.
- 1915-6: A clinical trial in adults receiving Linzess (linaclotide) to assess development of antidrug antibody (ADA) responses in patient samples. Validated assays capable of sensitively detecting ADA responses that may be present at the time of patient sampling, developed under PMR 1915-4 above, will be used. Sampling will occur at 0 and 2 weeks, and at 1, 3, 6, and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.

- 1915-7: A milk-only lactation trial in lactating women receiving Linzess (linaclotide) therapeutically to assess concentrations of linaclotide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Nursing Mothers' subsection of the labeling

This application triggered PREA for a different dosing regimen for the indication of CIC. The Pediatric Research Committee (PeRC) PREA subcommittee meeting was held on 10/19/2016, and the committee agreed with DGIEP that no additional studies were needed to evaluate the lower dosage strength. However, the PMRs associated with the original approval of this product apply to this application. In the original approval letter dated August 30, 2012, the pediatric study requirement for CIC in ages birth to six months was waived, and subsequently, in a letter dated July 16, 2014, the requirements from birth to under 2 years of age for CIC was waived as the study was no longer feasible due to safety concerns (the review of available data in the literature regarding GC-C ontogeny and the nonclinical study findings suggesting an age-dependency of the pharmacodynamic response indicate that it is not safe to administer linaclotide to children < 2 years of age). The FDA agreed to a deferral extension of a PMR to study children with CIC ages 2-17y on the basis of safety concerns in patient's age 2 to 5y (see 2.4.1 Severe Dehydration for further discussion). The PMR was released and separate PMRs to accommodate the age groups (2-5y and 6-17y) were provided in a letter dated 4/30/2015. After results of the animal studies for safety were reviewed it was determined that a study to measure GC-C mRNA levels in duodenal and colonic tissues should be required as a Safety PMR (2825-1: A study to measure GC-C mRNA levels in duodenal and colonic tissue obtained from children ages 0 to 6 years of age). Sections 2.4 Important Safety Issues With Consideration to Related Drugs and 7.6.3 Pediatrics and Assessment of Effects on Growth provide further discussion.

The current unfulfilled PREA PMRs for the CIC indication are listed below (the reader is referred to Table 36 for a complete list including protocol numbers and PMR status at the time of this writing):

- 2161-3: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 6 to 17 years treated with Linzess (linaclotide)
- 2161-2: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 2 to 5 years treated with Linzess (linaclotide).

A pediatric written request including, but not limited to, the above studies was issued in March 2016 (refer to DARRTS communication dated 3/11/2016).

2 Introduction and Regulatory Background

Chronic Idiopathic Constipation (CIC)¹, also referred to as functional constipation, is defined as a symptom-based disorder occurring over a chronic time course and characterized by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool². Patients with CIC also typically suffer from abdominal symptoms of varying severity, with no identifiable underlying cause (i.e., opioid use, mechanical obstruction, etc.). This disorder is one of the most common functional gastrointestinal disorders worldwide, with a prevalence of approximately 14%³. CIC is not associated with abnormal radiologic or endoscopic abnormalities, nor is it associated with biochemical abnormalities; diagnosis currently rests, therefore, on clinical signs and symptoms. Although a number of clinical definitions of CIC have been proposed, the criteria developed through the Rome process have been those most widely employed in clinical trials⁴. Rome III defines CIC as the presence of two or more of the following:

- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- Sensation of incomplete evacuation for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three defecations per week

These criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis⁵. There should be insufficient criteria for irritable bowel syndrome, and loose stools are rarely present without the use of laxatives. The current treatment options for CIC include three approved prescription therapies [linaclotide (Linzess®), lubiprostone (Amitiza®), and lactulose (which carries a more general constipation indication)], a variety of over-the-counter therapies (e.g., laxatives, stool softeners, enemas), dietary management, and behavioral therapy.

¹ The term chronic idiopathic constipation (CIC) is being used in this document; however, the terms CIC and functional constipation may be used interchangeably in clinical practice.

² Brandt LJ, Prather CM, Quigley EM et al. systematic review on the management of chronic constipation in North America. *Am J Gastroenterol* 2005;100 (Suppl 1): S5–S21.

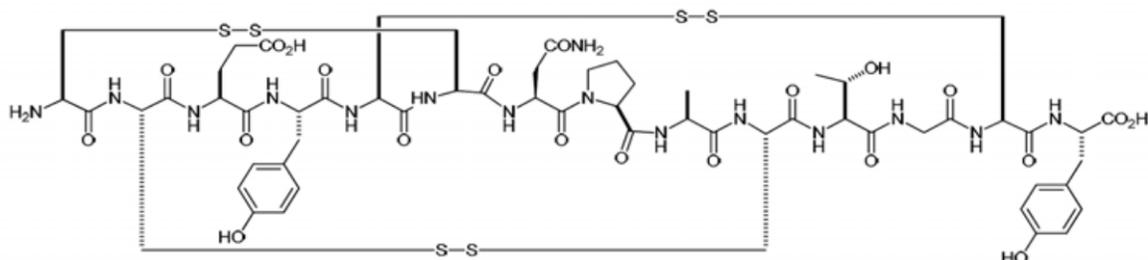
³ Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:1582–1591.

⁴ <http://www.nature.com/ajg/journal/v109/n1s/full/ajg2014187a.html>

⁵ Longstreth GF, Thompson WG, Chey WD et al. Functional bowel disorders. *Gastroenterology* 2006;130:1480–1491.

2.1 Product Information

Trade Name: Linzess®
Established name: linaclotide

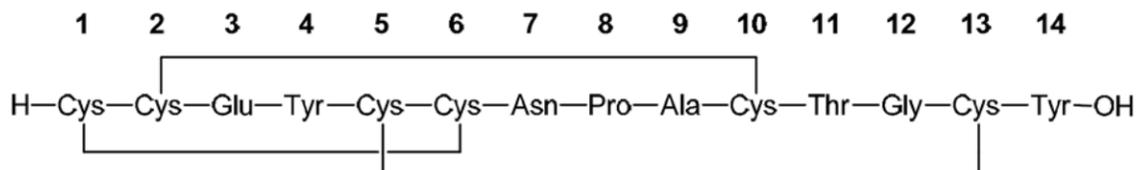


Molecular Formula: C₅₉H₇₉N₁₅O₂₁S₆

Average molecular mass: 1526.8 Daltons

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)

Amino Acid Sequence:



Pharmacologic Class: Guanylate cyclase-C (GC-C) receptor agonist

Route of Administration, Description, and Formulation: Linaclotide capsules are for oral administration. Linaclotide 145 ug is formulated as an oral hard gelatin capsule

(b) (4). 72 mcg capsules contain linaclotide-coated beads in hard gelatin capsules. The capsules are white to off-white opaque with gray imprint "FL 72".

2.2 Tables of Currently Available Treatments for Proposed Indications

Three prescription medications have been approved drugs for CIC; linaclotide (Linzess®), lubiprostone (Amitiza®), and tegaserod maleate (Zelnorm®). In addition, the prescription medication lactulose carries a more general constipation indication and may be used in the management of CIC. Serious safety concerns, namely ischemic cardiovascular events, have been associated with Zelnorm, leading to its withdrawal from the market in 2007. Zelnorm is currently available only through an expanded access program. Treatment for CIC also includes non-pharmacologic therapies such as dietary changes (e.g., increased fluid intake), manual evacuation, and behavioral

treatment (e.g., increased activity). Multiple over-the-counter medications are available for treatment of CIC as well, including stool softeners, bulk-forming laxatives, stimulant laxatives, saline osmotic laxatives, osmotic laxatives, lubricants, and other osmotic agents like polyethylene glycol (PEG) 3350 with electrolytes and PEG 3350 without electrolytes.

The above and other medications commonly used to treat CIC are listed in Table 1 below. Several over the counter products are available with different mechanisms of action.

Table 1 Current Available Treatments for CIC

Drug/Class	Indication	Comments
Prescription medications		
Linzess (linaclotide)	Rx for CIC and IBS-C in adults	-Locally acting GC-C agonist -Contraindicated in children <6y
Amitiza (lubiprostone)	Rx for CIC in adults, OIC ^a in adults with non-cancer pain, and IBS-C in adult women	-Locally acting chloride channel activator -Most common adverse effects pre-approval were headache and diarrhea
Zelnorm (tegaserod maleate)	Original Rx for CIC in adults <65y/o and IBS-C in women. Removed from the market in 2007 ^b	-Mimics serotonin -Available under restricted use/ expanded access under single patient treatment IND -Safety risk of ischemic CV events
Lactulose	Constipation	-Poorly absorbed synthetic disaccharide, increases colonic osmotic pressure resulting in increased fluid and peristalsis. -N/V/cramps have been reported; excessive dosage leads to diarrhea.
Over The Counter		
Hyperosmotic Laxative	OTC for constipation	-Draws fluid into the colon and increases stool volume. -PEG3350 with and without electrolytes, lactulose, sorbitol.
Bulk-forming Laxatives	OTC for constipation	-Absorbs fluid in the GI tract. -Fiber supplements usually made from bran e.g., psyllium, methylcellulose, polycarbophil.
Stimulant Laxatives	OTC for constipation	-Direct stimulation of colonic smooth muscle e.g., bisacodyl, senna, castor oil. -Many reformulated without phenolphthalein due to FDA concern of potential carcinogenicity.
Saline Laxatives	OTC for constipation	- Draws fluid into the small intestine e.g., sodium phosphate, magnesium citrate, magnesium hydroxide.

Lubricant Laxatives/Stool Softeners	OTC for constipation	-Mixes liquids into the stool facilitating easy passage e.g., docusate, mineral oil, glycerin
Enemas	OTC for constipation	-Mechanical distention of bowel resulting in stool evacuation.

^aOpioid-induced constipation

^b<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm>

Source: Reviewer's Table

2.3 Availability of Proposed Active Ingredient in the United States

Linaclotide was approved on August 30, 2012 for the treatment of Chronic Idiopathic Constipation(CIC) in adults at the 145 ug once daily dose and Irritable Bowel Syndrome with Constipation(IBS-C) in adults at the 290 ug once daily dose.

2.4 Important Safety Issues With Consideration to Related Drugs

2.4.1 Severe Dehydration

As described in the nonclinical review of the original NDA for linaclotide, neonatal/juvenile mice oral toxicity studies revealed that young mice are particularly sensitive to linaclotide toxicity, and a lethality signal was observed which was highly age-dependent. As a result of these nonclinical juvenile toxicity findings, DGIEP required a PMR to investigate the mechanism of lethality in neonatal and juvenile mice treated with linaclotide. Results from this study were considered to be crucial in informing the potential risk of linaclotide as well as the design of future clinical studies in the pediatric population. The reader is referred to the nonclinical review by Yuk-Chow Ng, Ph.D. and David B. Joseph, Ph.D. signed 01/14/2014 for a detailed review of these nonclinical studies. The nonclinical reviewers determined that "...these data strongly suggest that the deaths which occur after linaclotide administration in neonatal mice are a consequence of exaggerated GC-C agonist pharmacology, resulting in a significant fluid shift into the intestine leading to severe dehydration and death." These nonclinical study findings, suggesting an age-dependency of the pharmacodynamic response, indicate that it is not safe to administer linaclotide to children < 2 years of age. A PMR to measure GC-C mRNA levels in duodenal and colonic tissue in children ages 0 to 6 years of age is currently ongoing to determine the potential risk of a significant fluid shift into the intestine based on linaclotide toxicology studies conducted in juvenile mice, and published research indicating increased expression of the target receptor (GC-C) in children; a greater number of receptors are present in infants and the number decreases with increasing age⁶. Measurement of GC-C mRNA levels appear to be the

⁶ Cohen, MB, Guarino, A, Shukla, R, Gianella, RA. Age-Related Differences in Receptors for Escherichia coli Heat-

most sensitive approach for evaluating GC-C expression and has been reported to correlate well with GC-C density on the surface of the intestinal epithelium⁷. Results from the GC-C mRNA study as well as results from the ongoing CIC clinical trial (LIN-MD-62) of children ages 6-17 years of age will inform the trial design for a phase 2 CIC study in children ages 2-5 years of age. Currently and until such time that this concern is addressed, there is a boxed warning in the labeling with a contraindication in pediatric patients up to 6 years, and use of linaclotide in pediatric patients 6 through 17 years of age is to be avoided.

2.4.2 Immunogenicity and Guanylin Deficiency

Due to linaclotide's structural homology to endogenous guanylin peptide family members, development of anti-drug antibodies could cross react with endogenous guanylin peptides that could lead to deficiency syndromes. During review of the original NDA application, concerns were raised regarding the potential immunogenicity of linaclotide. Linaclotide is a small peptide product with multiple attributes that make it potentially immunogenic, including 3 disulphide bonds which render a more rigid tertiary structure than is typical for a 14 amino acid peptide. In addition, the ideal T cell epitopes for activation via HLA class 2 pathway are 12-18 amino acids in length, and for the HLA class 1 pathway the epitopes are at least 9 amino acids in length. Therefore, linaclotide contains an appropriate number of amino acids to serve as a T cell epitope for either pathway. Adverse events associated with antibodies to guanylin could theoretically manifest as hypernatremia, volume overload, hypertension, and constipation⁸. At the time of original review, the NDA safety database was specifically examined for evidence of peripheral edema, pulmonary edema, fluid retention, hypertension, and hypernatremia. No evidence of a signal of clinical deficiency syndromes was identified in the clinical safety dataset submitted with original NDA. However, in order to identify unexpected serious risks associated with the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and lead to deficiency syndromes, FDA determined that the Applicant was required to conduct PMRs to develop and validate assays for the detection of anti-linaclotide antibodies, including IgM, IgG and IgA, that may be present in the serum at the time of patient sampling, as well as a clinical trial in adults receiving linaclotide to assess development of anti-drug antibody (ADA) responses in patient samples. The Applicant has reported

(b) (4)

fulfill the remaining portions of the PMR, and this has resulted in missed milestones. The reader is referred to Section 7.4.6 Immunogenicity for further discussion. At the time of this writing, no specific safety pattern is identified from the available post-marketing data, and no clinical signal has thus far been identified in the clinical

Stable Enterotoxin in the Small and Large Intestine of Children. *Gastroenterology* 1988;94:367-73
7 Carrithers SL, Parkinson SJ, Goldstein SD, Park PK, Urbanski RW, Waldman SA. Escherichia coli heat-stable enterotoxin receptors. A novel marker for colorectal tumors. *Dis Colon Rectum*. 1996 Feb;39(2):171-81.

⁸ NRF, F. M. (2011). Guanylin peptide family: history, interaction with ANP, and new pharmacological perspectives. *Can J Physiol. Pharmacol.*, 89:575-585.

development program for linaclotide. The reader is referred to Section 7.3.5.2 Guanylin Deficiency for further discussion.

2.4.3 Diarrhea

Prescription products being developed for CIC and IBS-C have been associated with severe diarrhea resulting in dehydration and electrolyte abnormalities, and associated sequelae. Per the current prescribing information⁹ for linaclotide, diarrhea was the most common adverse reaction of linaclotide-treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. Severe diarrhea was reported in 2% of the linaclotide-treated patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summary focuses on regulatory activity following the original approval for Linzess® that took place on August 30, 2012. Please refer to Dr. Erica Wynn's Clinical Review, Section 2.5 and Appendix 9.2, dated August 2, 2012 for summary of regulatory activity prior to this date.

Table 2 summarizes labeling supplements that have been approved for linaclotide since original approval:

⁹ <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=09beda19-56d6-4a56-afdc-9a77b70b2ef3>

Table 2 Prior Approval Supplements

Approval Date	Summary of Changes
August 8, 2013	Addition of language to the LINZESS prescribing information and the Medication Guide providing additional patient instructions on how to take Linzess; specifically, what to do if a patient misses a dose. Several editorial changes throughout the prescribing information and Medication Guide.
July 9, 2014	Updates on the following sections of the Package Insert incorporating new data from recently completed nonclinical studies that elucidate the mechanism of death in neonatal and juvenile mice and the effects of linaclotide in older juvenile mice: •Boxed Warning •Contraindications (4) •Warnings and Precautions, Pediatric Risk (5.1) •Warnings and Precautions, Diarrhea (5.2) •Use in Specific Populations, Pediatric Use (8.4) •Nonclinical, Animal Toxicology and/or Pharmacology (13.2) •Patient Counseling Information (17)
November 23, 2015	Addition of language to Section 2 Dosage and Administration and Section 17 Patient Counseling Information of the PI allowing for the option to sprinkle capsule contents in applesauce or in water, and labeling language for patients using a nasogastric (NG) or gastric (G) feeding tube.
April 16, 2016	Addition of information on the effects of linaclotide on SBM frequency, stool consistency, and straining in Section 14 Clinical Trials of the PI ^a .

^apackage insert

Source: Reviewer's Table

Manufacturing changes or additions also were approved on the following dates:

- 11/8/2013: Change in the name of the specified impurity (b) (4) discovered in one of the drug substance impurity methods and the drug product impurity method.
- 7/1/2014: Addition of an alternate analytical testing site, (b) (4) for mass spectrometric analysis of linaclotide drug substance.
- 12/11/2014: Increase in batch size (b) (4) for the 145 mcg strength, and Change in the validated (b) (4)
- 5/18/2016: Addition of (b) (4) as an alternate manufacturing site for linaclotide drug substance.

A single Type C meeting took place between the Division of Gastroenterology and Inborn Errors Products (DGIEP) and Ironwood Pharmaceuticals, Inc. on September 9, 2014 to discuss the study design and regulatory plans for the single proposed phase 3 clinical trial (MCP-103-309) to support approval of a 72ug dose of linaclotide for CIC patients. Multiple issues were discussed, including, but not limited to, the primary/secondary endpoints, design of the trial, and proposed labeling. A summary of the important agreements and points discussed follow.

- 1) Regarding the proposed primary endpoint (A CSBM overall responder is a patient who meets the criteria of being a CSBM weekly responder for 9 out of the 12 treatment weeks. A CSBM weekly responder is a patient who has a CSBM frequency during the treatment week that is at least 3 CSBMs/week and increases by at least 1 CSBM/week from Pre-Treatment), the Division recommended that in order to establish durability of response, the criterion that out of the 9 weeks of weekly CSBM response, at least 3 weeks should occur in the last 4 weeks of the 12-week treatment period, should be added.
- 2) Regarding the secondary endpoints, it was recommended that secondary analyses of monthly responders for each month (e.g., responder for 3 out of 4 weeks) should also be presented.
- 3) DGIEP found the proposed safety measures to be generally acceptable.
- 4) The Applicant proposed to add that (b) (4) to the *Dosage and Administration* section of the PI. DGIEP disagreed with this proposed language because although (b) (4) are defined and assessed in a clinical trial setting, in clinical practice patients with CIC are likely to be using laxatives *as needed*. Therefore, unless suitable evidence could be provided to the contrary, patient recall of the number of weekly (b) (4) bowel movements would seem unreliable in clinical practice. The Applicant proposed addressing the Agency's concern with a proposed altering of the labeling text to (b) (4).
- 5) The Applicant proposed that one adequate and well-controlled phase 3 trial as well as the supportive data from the pivotal phase 3 CIC trials and the phase 2b MCP-103-201 study, are sufficient to support approval of the 72 ug dose of linaclotide. DGIEP responded that this could be sufficient to support submission of a supplemental NDA for the 72 ug dose of linaclotide for the treatment of CIC in adults. However, whether this single additional trial will provide substantial evidence of efficacy to support approval of the 72 ug dose of linaclotide for the treatment of CIC in adults will be a review issue.
- 6) DGIEP also recommended that the Applicant consider designing the trial to evaluate efficacy of a higher dose (145 ug) in patients who do not respond to the 72 ug dose (e.g., after ≥ 4 failed weeks). Similarly, the trial could explore dose reduction in those patients who have diarrhea on the 145 ug dose.

In addition, multiple meetings and correspondences took place under IND 63290 with regards to the following PMR under FDAAA that was included in the Approval Letter.

- 1915-4 Develop and validate sensitive and precise assays for the detection of antilinaclotide antibodies, including IgM, IgG and IgA, that may be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

The Applicant failed to meet the deadline for PMR 1915-4 (March 2014) and requested additional time to complete this study, (b) (4)



The sponsor is planning to submit the final report in early 2017.

Correspondence related to PMR 1915-4 included:



Please see Section 7.3.5.2 Guanylin Deficiency for further discussion of this safety issue.

2.6 Other Relevant Background Information

The Applicant developed linaclotide under IND 063290.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Methods used to evaluate data quality and integrity included:

- Review of possible bias based on financial ties
- Seeking source documentation for efficacy analyses
- Evaluation of safety data by reviewing JMP datasets, case report forms, narratives, and verbatim terms, JReview, and MAED
- Review of Sponsor's compliance with Good Clinical Practices

3.2 Compliance with Good Clinical Practices

According to the sponsor, this study was conducted in full compliance with the United States (US) Food and Drug Administration (FDA) guidelines for Good Clinical Practices (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR § 312.120. The trial protocol (and any amendments), Informed Consent Form (ICF), and associated documentation were approved by the IRB prior to trial initiation.

Reviewer comments: The clinical trial appeared to be conducted in accordance with acceptable ethical standards and informed consent.

The numbers of patients with major protocol deviations are summarized in Table 3.

Table 3 Number and Percentage of Patients with Protocol Deviation by Deviation Category (Randomized Population)

	N=1223
Deviation Category	n (%)
Entered study but didn't satisfy entry criteria	40 (3.3)
Patients met predefined withdrawal criteria and remained on study	n/a*
Received the wrong treatment or incorrect dose	2 (0.2)
Received an excluded concomitant medication	21 (1.7)

* not applicable for this report because the MCP-103-309 protocol did not have pre-defined withdrawal criteria
Data source: [Appendix 16.2.2](#)
IVRS = interactive voice response system; eCRF = electronic case report form

Source: Reproduced from Applicant's CSR, pg. 91

Two patients were dispensed kits containing study drug intended for another patient in the trial. In each case, the error was discovered by study staff and the patient returned the incorrectly dispensed study drug to the clinic and received their assigned study drug. A clinical review of these protocol deviations by the Applicant did not indicate any impact on the efficacy or safety conclusions of the study.

The Applicant also conducted site-level and region-level analyses for key efficacy and safety data to identify "extreme or opposite results" per the ICH E3 guidance. Among the five geographic regions, the Applicant reports that there were no differences observed in demographics, patient baseline characteristics, or study conduct (including protocol deviations, IVRS compliance, and dosing compliance) that were considered likely to have impacted the overall trial conclusions. However, CSBM responder rates and change-from-baseline scores were lower in the Southeast Region than in the other four geographic regions. This data was also reviewed at the site level. Among the 21 sites that enrolled at least 15 patients in the trial (and were therefore deemed large enough to potentially impact overall trial results), there were no differences observed in demographics, patient baseline characteristics, or study conduct (including protocol deviations, IVRS compliance, and dosing compliance) that were considered likely to have impacted the overall trial conclusions. However, eight of these sites were noted to have low CSBM Overall Responder rates and low TEAE rates relative to the overall ITT Population. Six of these sites were in the Southeast Region (Site #s 002, 006, 016, 052, 056, and 061) and two were in the West Region (Site #s 003 and 018). Additional and supplemental review of site monitoring reports from the eight sites listed above were conducted by the Applicant and did not appear to reveal any clinical conduct issues that could have impacted trial results. Site audits were conducted by the Applicant at four of the sites, including two performed during the trial and two performed following trial completion and unblinding. Results from these audits did not identify any significant study conduct or data integrity issues.

Reviewer comments: The Applicant concludes that although the eight above identified sites appear to have results that are different from the other sites in this trial, the results of their review indicate that the data produced by these sites, as well as all other sites in the trial, were collected in accordance with the protocol and GCP. In addition, these sites reported CSBM responder rates that did not favor linaclotide; therefore, additional sensitivity analyses excluding these sites would not be necessary as they would not be expected to bias the primary efficacy analysis towards a positive treatment effect. This reviewer agrees with the Applicant's assessment.

A request for Office of Scientific Investigations (OSI) audit was placed for this sNDA. No sites were chosen for inspection after reviewing enrollment, efficacy outcome, previous inspectional history, and protocol violations. For details, please see Clinical Inspection Summary (CIS) by OSI medical officer Dr. Susan Leibenhaut.

3.3 Financial Disclosures

One investigator disclosed a financial interest as follows:

- (b) (6) - Study MCP-103-309 (site (b) (6), principal investigator): For the year ending (b) (6), (b) (6) was a member of the speaker's bureau for the drug Linzess and earned greater than \$25,000 given his national and international expertise in this area. As a former PI of the original clinical trials and a pre-clinical investigator for linaclotide, he played an important role in measuring the effects of linaclotide on visceral sensation.

Reviewer comments: The Applicant reports that bias has been minimized in this study due to a number of critical elements that were built into the design of the phase 3 clinical study. These design elements are described below:

- *Multicenter, double-blinded, randomized, placebo-controlled design.*
- *Patient enrollment and treatment assignment were accomplished using a centralized process.*
- *Data contributing to efficacy endpoints (patient diary information) were collected using a centralized CRO-monitored interactive voice response system (IVRS). Data were entered directly by the patients.*
- *The statistical analyses for the study were prospectively defined by the Sponsor. In order to minimize bias, the analysis for each efficacy endpoint was based on an Intent-to-Treat study population.*

The disclosed financial interests/arrangement does not appear to affect the approvability of the application or raise questions about data integrity; this investigator's site screened one patient who failed to be randomized, and therefore did not influence

the efficacy results as it provided minimal contribution to study data. For more details, see Appendix 9.5 Financial Disclosure Template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Each capsule contains 72 ug of linaclotide, a guanylate cyclase (GC-C) receptor agonist that is structurally related to the endogenous guanylin peptide family. The drug is metabolized in the gastrointestinal tract to a single active primary metabolite. The primary metabolite, MM-419447, is a 13-amino acid peptide lacking the C-terminal tyrosine that is present in linaclotide. Both linaclotide and its active metabolite bind to and activate the GC-C receptor locally, on the luminal surface of the intestinal epithelium.

Reviewer comments: Per the CMC reviewer, this supplement is recommended for approval from the CMC standpoint; please see the Dr. Hossein Khorshidi's review for details.

4.2 Clinical Microbiology

The Sponsor submitted no microbiology data for review.

4.3 Nonclinical Pharmacology/Toxicology

The Sponsor submitted no nonclinical study data for review.

4.4 Clinical Pharmacology/Pharmacometrics

No relative bioavailability (BA) or bioequivalence (BE) studies were performed in support of the 72ug dose.

Concomitant medication use was recorded during the Screening Visit through the EOT Visit, and Table 4 below summarizes the most common ($\geq 5\%$ of patients in any treatment group) concomitant medications taken by patients during the Treatment Period.

Table 4 Most Common ($\geq 5\%$ by ATC4 Preferred Term in any Treatment Group) Concomitant Medications (Safety Population)

Concomitant Medication (Preferred Term)	Placebo (N=401) n (%)	Linaclotide		Total (N=1223) n (%)
		72 ug (N=411) n (%)	145 ug (N=411) n (%)	
Any medication	260 (64.8)	265 (64.5)	251 (61.1)	776 (63.5)
Ibuprofen	24 (6.0)	54 (13.1)	28 (6.8)	106 (8.7)
Vitamins NOS	30 (7.5)	35 (8.5)	36 (8.8)	101 (8.3)
Lisinopril	29 (7.2)	27 (6.6)	31 (7.5)	87 (7.1)
Acetylsalicylic acid	20 (5.0)	29 (7.1)	34 (8.3)	83 (6.8)
Hydrochlorothiazide	28 (7.0)	26 (6.3)	29 (7.1)	83 (6.8)
Omeprazole	27 (6.7)	24 (5.8)	26 (6.3)	77 (6.3)
Paracetamol	22 (5.5)	26 (6.3)	22 (5.4)	70 (5.7)
Metformin	30 (7.5)	13 (3.2)	17 (4.1)	60 (4.9)
Vitamin D NOS	16 (4.0)	27 (6.6)	13 (3.2)	56 (4.6)
Levothyroxin	15 (3.7)	13 (3.2)	26 (6.3)	54 (4.4)
Fish oil	12 (3.0)	23 (5.6)	15 (3.6)	50 (4.1)

Data source: Section 14, Table 14.3.2.2
NOS=not otherwise specified

Source: Applicant's CSR dated 2/26/16, pg. 95

Reviewer comments: Ibuprofen was taken in approximately double the number of patients in the 72ug group compared to placebo and the 145ug dose group. The rest of the concomitant medications were generally balanced across treatment groups.

Please see Dr. Sandhya Apparaju's Clinical Pharmacology review from the original application submission for linaclotide dated 4/6/2012.

A pharmacometrics review was conducted to evaluate the effect of baseline characteristics on the dose-relationship of linaclotide across both the phase 3 trial MCP-103-309 and the phase 2b dose-ranging trial MCP-103-201. According to the pharmacometrics review, there appeared to exist a somewhat different dose-response relationship in the 2 trials when examined by baseline characteristics (the phase 2b data did not show a consistent relationship by dose). The reviewer states that this difference could be due to the varying treatment durations of the 2 studies, in addition to the other baseline characteristics of the treated population. Overall, the reviewer concludes that "the proposed dose of 72 mcg QD appears to have similar effect compared to 145 mcg for the treatment of patients with CIC. This effect is consistent for both less and more symptomatic treatment population with both doses demonstrating treatment effect. Therefore, the results of study 309 support the approval 72 mcg QD for CIC." The reader is referred to Dr. Eun Jee Lee's pharmacometrics review dated 12/2/2016 for details.

Reviewer comments: Per the Applicant, concentrations of linaclotide and its metabolite, MM-419447, are generally undetectable following oral administration and, therefore, standard pharmacokinetic (PK) parameters cannot be calculated.

4.4.1 Mechanism of Action

Linaclotide is a locally acting 14-amino acid peptide, which binds to and activates

GC-C on the luminal surface of the intestinal epithelium. Linaclotide acts by specifically activating intestinal GC-C, resulting in increased cyclic guanosine monophosphate (cGMP) production, which in turn causes chloride and bicarbonate to be secreted into the intestinal lumen with consequent increased fluid secretion and accelerated intestinal transit. Linaclotide has been shown to reduce visceral hypersensitivity in animal models. Activation of GC-C results in an increase in concentrations of cGMP, both extracellularly and intracellularly. Extracellular cGMP decreases pain-fiber activity, resulting in reduced visceral pain. Intracellular cGMP causes secretion of chloride and bicarbonate into the intestinal lumen, through activation of the cystic fibrosis transmembrane conductance regulator (CFTR), which results in increased intestinal luminal fluid and accelerated transit.

4.4.2 Pharmacodynamics

There were no new clinical pharmacology studies in human subjects in this efficacy supplement. However, the Applicant did provide study results from MCP-103-201 that demonstrated changes from baseline in SBM frequency rates, CSBM frequency rates, stool consistence, and straining, as well as assessed overall SBM and CSBM responders. These findings are further discussed in Section 6.1.4 Analysis of Primary Endpoint(s) and Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.

4.4.3 Pharmacokinetics

The Applicant conducted no further pharmacokinetics studies for this sNDA.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5 Clinical Trials Submitted to Support sNDA

<i>Trial ID</i>	<i>Trial Design</i>	<i>Product Dose and Route</i>	<i>Total N randomized</i>	<i>N Subjects Treated/Completed</i>	<i>Key Inclusion Criteria</i>
<i>Location (No. of Centers)</i>	<i>Duration of Treatment</i>				
MCP-103-309 US 105 Centers	Phase 3, DB, R, PC, PG 12 weeks	<u>Linaclotide</u> 72 ug QD 145 ug QD	1223	<u>Linaclotide</u> 411/369 72 ug QD, 411/352 145 ug QD	Age ≥ 18 y, met modified ^a Rome III criteria for CIC
		Placebo QD		Placebo QD 401/357	
MCP-103-201	Phase 2b, DB, R, PC, PG 4 weeks	<u>Linaclotide</u> 72 ug QD 145 ug QD 290 ug QD 579 ug QD	309	<u>Linaclotide</u> 59 72 ug QD, 56 145 ug QD, 62 290 ug QD, 63 579 ug QD	Age ≥ 18 y, met modified Rome II criteria for CIC
		Placebo QD		Placebo QD 69	

Source: Reviewer's table, modified from Applicant's Table 2-1, page 18, Summary of Clinical Safety.

^aOmits the following from Rome III criteria: Sensation of anorectal obstruction/blockage for at least 25% of defecations, Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)

For additional sources of clinical data that support the original application, please refer to Dr. Erica Wynn's clinical review dated 8/2/2012, Section 5.1, Table 2, page 36-7.

5.2 Review Strategy

For this supplemental NDA submission, Study MCP-103-309 was reviewed in detail. This study was designed to assess the efficacy and safety of linaclotide 72 ug

administered once daily to patients with chronic idiopathic constipation (CIC). The trial design will be reviewed in Section 5.3 Discussion of Individual Studies/Clinical Trials. Study results are discussed in Sections 6 (efficacy) and 7 (safety).

Study MCP103-201 is a phase 2b dose-ranging trial that provides supportive evidence and independent substantiation of the effects of linaclotide 72 ug in CIC. This trial is briefly described in Section 5.3. Study results are discussed in Sections 6 (efficacy) and 7 (safety).

The Applicant conducted only one adequate and well-controlled trial to support the 72ug dose. Based on the Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, this may be acceptable given that the single trial was large, multi-center, and statistically persuasive. In addition, data from other approved doses for the same indication and supportive data from a phase 2b trial for the 72ug dose may be in part relied upon. For further discussion regarding the basis for relying on one trial, see Section 6.1.10 Additional Efficacy Issues/Analyses.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical development program for linaclotide that resulted in FDA approval of linaclotide 145 ug for use in patients with CIC included 2 large double-blind, placebo-controlled registration trials (MCP-103-303 and LIN-MD-01) and a phase 2b dose-range-finding trial (MCP-103-201) that also evaluated a 72 ug dose. The overall design of the phase pivotal 3 trials was identical through the 12-week Treatment Period. LIN-MD-01, which enrolled 633 patients, and MCP-103-303, which enrolled 643 patients, evaluated the safety and efficacy of 2 doses of linaclotide: 145 ug (the dose subsequently approved by FDA for this indication) and 290 ug, administered as oral capsules. For details regarding studies LIN-MD-01 and MCP-103-303, please refer to Dr. Erica Wynn's NDA review dated 8/2/2012, Section 5.3.

In support of this supplemental application, the Applicant conducted an additional Phase 3 trial, MCP-103-309, to evaluate the safety and efficacy of a lower dosage strength, 72ug, for linaclotide. The Applicant also provided supportive information from a phase 2b trial, MCP-103-201. The protocol summaries for both trials are provided below in Section 5.3.1 and Section 5.3.2, respectively.

5.3.1 Protocol Summary, Study MCP-103-309

5.3.1.1 Title

Study MCP-103-309: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide (72 ug or 145 ug) Administered Orally for 12 Weeks to Patients with Chronic Idiopathic Constipation

5.3.1.2 Study Design and Objectives

MCP-103-309 was a multicenter, randomized, double-blind, placebo-controlled, parallel group, multiple-dose, 12-week trial conducted in patients with chronic idiopathic constipation (CIC) confirmed using modified Rome III diagnostic criteria. It consisted of a screening period of up to 21 days, pretreatment period of 14 to 21 days, a 12-week treatment period, and an End of Treatment visit. The total study duration was 130 days. Patients were randomized to treatment through a central randomization and were stratified by baseline SBM frequency (i.e., those with > 1 SBM/week and those with ≤ 1 SBM/week).

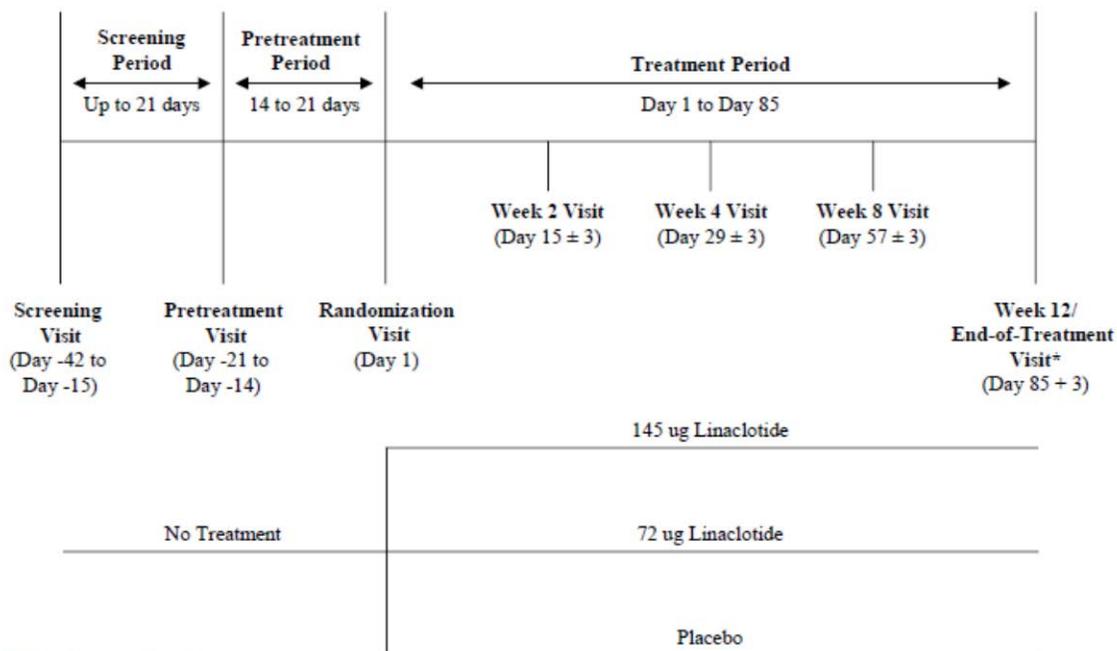
Reviewer comments: Phase 3 trial MCP-103-309 was nearly identical in overall design to the first 12 weeks of the two Phase 3 registration trials for linaclotide 145 ug (MCP 103-303 and LIN-MD-01).

Primary Objective:

- To determine the efficacy and safety of linaclotide 72 ug administered once daily to patients with CIC.

MCP-103-309's study design is presented in Figure 1.

Figure 1 Study Design



Note: there is no Day 0

* This visit represents the end of the study

Source: Reproduced from Sponsor's CSR pg. 31

5.3.1.3 Eligibility Criteria

Diagnostic Criteria included:

Subjects had to meet the modified Rome III criteria for diagnosis of CIC:

< 3 SBMs per week and reported 1 or more of the following symptoms during the 3 months before the diagnosis with the onset at least 6 months before the diagnosis:

- straining during $\geq 25\%$ of BMs
- lumpy or hard stools during $\geq 25\%$ of BMs, and
- a sensation of incomplete evacuation during $\geq 25\%$ of BMs.

The following components of the original Rome III criteria were omitted from the modified criteria listed above:

- sensation of anorectal obstruction/blockage for at least 25% of defecations
- manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)

Key Inclusion Criteria included:

- Adults 18 years or older
- CIC confirmed by the modified Rome III diagnostic criteria
- During the 14 calendar days prior to randomization, the subject reported an average of < 3 complete spontaneous BMs (CSBMs) and ≤ 6 SBMs per week by the IVRS (Note: A CSBM is an SBM that is associated with a sense of complete evacuation. An SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM as evidenced by the patient reported concomitant medicine use via the IVRS.)
- Met the colonoscopy requirements defined by the American Gastroenterological Association guidelines
- Willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine (bisacodyl tablets or suppositories)
- Agreed to refrain from making any new, major life-style changes that may have affected CIC symptoms (e.g., starting a new diet or changing his or her exercise pattern) from the time of signature of the ICF to the last trial visit.

Key Exclusion Criteria included:

- Reported loose (mushy) or watery stools (Bristol Stool Form Scale [BSFS] score of 6 or 7) in the absence of any laxative, suppository, enema, or prohibited medicine for > 25% of BMs during the 12 weeks before the Screening Visit
- Met the Rome III criteria for IBS: reported abdominal discomfort or pain at least 3 days/month during the 3 months before the Screening Visit with the onset at least 6 months before the Screening Visit associated with two or more of the following features:
 - Relieved with defecation
 - Onset associated with a change in frequency of stool
 - Onset associated with a change in form (appearance) of stool
- Structural abnormality of the GI tract or a disease or condition that could affect GI motility
- Diagnosis or family history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer
- Received a diagnosis of inflammatory bowel disease (IBD)
- Unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, weight loss) or systemic signs of infection or colitis
- Current active peptic ulcer disease (i.e., disease that was not adequately treated or stable with therapy)
- History of diverticulitis or any chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis) that could be associated with abdominal pain or discomfort and could confound the assessments in this trial, unless the patient was considered to have been cured of the condition
- Potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis)

- Any of the following diseases or conditions that could be associated with constipation: pseudo-obstruction, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis
- Fecal impaction that required hospitalization or emergency room treatment, or had a history of cathartic colon, laxative or enema abuse, ischemic colitis, or pelvic floor dysfunction (unless successful treatment had been documented by a normal balloon expulsion test)
- Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit, surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit, an appendectomy or cholecystectomy during the 60 days before the Screening Visit, other major surgery during the 30 days before the Screening Visit
- History of cancer other than treated basal cell or squamous cell carcinoma of the skin. (Note: Patients with a history of cancer were allowed provided that the malignancy had been in a complete remission for at least 5 years before the Randomization Visit. A complete remission was defined as the disappearance of all signs of cancer in response to treatment.)
- History of diabetic neuropathy
- Untreated hypothyroidism or treated hypothyroidism for which the dose of thyroid hormone had not been stable for at least 6 weeks at the time of the Screening Visit
- Reported a BSFS score of 6 (loose, mushy stools) for > 1 SBM or a BSFS score of 7 (watery stools) with any SBM over the 14 calendar days before the Randomization Visit
- Used Rescue Medicine (bisacodyl tablet or suppository) or any other laxative, suppository, or enema, on the calendar day before or the calendar day of the start of the Treatment Period
- Reported using a Prohibited Medicine (excluding laxatives, suppositories, and enemas) during the Pretreatment Period or was not willing or able to abide by the restrictions regarding use of Prohibited Medicines (Note: The use of fiber, bulk laxatives, or stool softeners [such as docusate] was acceptable provided the patient had been on a stable dose during the 30 days before the Screening Visit and planned to continue on a stable dose throughout the trial.).

Prior, Rescue, and Concomitant Therapies:

Prior medication was defined as any medication taken before the date of the first dose of double blind study drug. Concomitant medication was defined as any medication taken on or after the date of the first dose of double-blind study drug during the Treatment Period. Medications started after the date of the last dose of double-blind study drug were not considered concomitant medications.

Rescue Medicine, which was selected by and dispensed to patients, was a choice of 5-mg bisacodyl tablets or 10-mg bisacodyl suppositories. During the Pretreatment and Treatment Periods patients could use Rescue Medicine when at least 72 hours had passed since their previous BM or when their symptoms became intolerable. In order to qualify for randomization into the Treatment Period however, patients could not use Rescue Medicine on the calendar day before the Randomization Visit or on the day of the Randomization Visit up until the time of the clinic visit. Patients must have agreed to refrain from using Rescue Medicine from the time they arrived at the clinic for the Randomization Visit through the calendar day after randomization.

Patients were assessed on the day of any rescue medicine use with the following:

-“Have you taken any laxatives, suppositories or enemas since yesterday’s call?”

1=Yes

2=No

-“Was this rescue medication use today, yesterday, or both today and yesterday?”

1=Today

2=Yesterday

3=Both Today and Yesterday

At the Screening Visit, all ongoing medicines or investigational products taken by the patient, including past use of CIC prescription medicines, tegaserod (Zelnorm®), prucalopride, plecanatide, linaclotide (Linzess®), and lubiprostone (Amitiza®), even if not ongoing at the time of the Screening Visit, were recorded. Any over-the-counter or prescription laxatives, suppositories, or enemas used to treat CIC or diarrhea were not allowed during the Pretreatment and Treatment Periods, or on the calendar day before the Pretreatment Visit. A complete list of drugs that were conditionally allowed and drugs that were not allowed as concomitant medicines for either episodic or chronic use or as Rescue Medicine is provided in Appendix 9.4 Prohibited Medicine.

5.3.1.4 Treatment

Patients were randomized 1:1:1 through a central randomization and were stratified by baseline SBM frequency (i.e., those with > 1 SBM/week and those with ≤ 1 SBM/week). Patients received linaclotide 72ug, linaclotide 145ug, or placebo treatment once daily in the morning at least 30 minutes before breakfast.

Reviewer comments: Dose selection was based on clinical results from the Phase 2b dose-range-finding trial (MCP-103-201), which evaluated daily linaclotide doses of 72, 145, 290, and 579 ug versus placebo. In this study, linaclotide 72 ug was reported to demonstrate efficacy over placebo and also had a lower incidence of diarrhea than linaclotide 145 ug; thus linaclotide 72 ug was chosen for evaluation in the MCP-103-309 trial. The approved dose of 145ug was included as a positive control. The Applicant

also provides rationale that patients with CIC suffer from a range of bowel symptoms of varying severities, may require individualized approaches to the management of their symptoms, may differ in their responsiveness to treatment with linaclotide in clinical practice, and that practicing physicians have suggested that the availability of a lower dose of linaclotide may be helpful in the clinical care of some CIC patients. Therefore, the Applicant has studied the safety and efficacy of 72 mcg of linaclotide and are seeking approval of this dose.

5.3.1.5 Study Visits and Procedures

During the Pretreatment and Treatment Periods, patients were asked to call the IVRS at approximately the same time each day. During these calls, patients were to provide certain information daily and other information weekly, as specified below.

Daily Assessments: The following information was to be provided to the IVRS each day:

- Daily Bowel Habits (the following information was to be collected for each bowel movement [BM]):
 - The day of the BM
 - Whether the BM was associated with a sense of a complete evacuation
 - Stool consistency on the Bristol Stool Form Scale (BSFS)
 - Straining on a 5-point ordinal scale
- Daily Patient Symptom Severity Assessments:
 - Rating of abdominal pain at its worst during the previous 24 hours on a 0-to-10 point numerical rating scale (NRS)
 - Rating of abdominal discomfort during the previous 24 hours on a 0-to-10 point NRS
 - Rating of abdominal bloating during the previous 24 hours on a 0-to-10 point NRS

The study was comprised of 7 Study Visits, as illustrated in the Schedule of Events (presented by study phase in Section 5.3.1.6 Study Phases) and in the following brief summary:

Screening Visit (Visit 1)

A review of inclusion/exclusion criteria was to be conducted to determine the patient's eligibility for progression to the Pretreatment Period. Medical history, physical exam, body weight/height, vital signs, documentation of prior and concomitant medicines, and collection of blood/urine samples were to be performed.

Pretreatment Visit (Visit 2)

Pretreatment Period data was to be collected to determine whether the patient was eligible to continue into the Treatment Period of the trial, to provide the patient with experience using the data collection methods employed during the trial (i.e., IVRS), and for comparison with data collected during and after treatment. Verification of

inclusion/exclusion criteria, body weight/vital signs measurement, documentation of concomitant medicines, review of AEs, dispensing of rescue medicines, and IVRS training was to be performed.

Randomization Visit (Visit 3)

Verification of inclusion/exclusion criteria, body weight/vital signs measurement, documentation of concomitant medicines, collection of blood/urine samples, review of AEs, IVRS assessments, and SBM baseline frequency recall question were performed before randomization and administration of the first dose of study drug at the trial center. In addition, PAC-QOL, EQ-5D, WPAI:C were to be performed after randomization (prior to first dose).

Week 2 Visit (Visit 4)

Body weight/vital signs measurement, documentation of concomitant medicines, review of AEs, completion of diarrhea questionnaire if applicable, dispensing of rescue medicines, IVRS compliance verification and reminder, and treatment satisfaction assessment were to be performed.

Week 4 Visit (Visit 5)

Body weight/vital signs measurement, documentation of concomitant medicines, review of AEs, completion of diarrhea questionnaire if applicable, study drug accountability and dispensing, dispensing of rescue medicine as needed, IVRS compliance verification and reminder, PAC-QOL, EQ-5D, WPAI:C, and treatment satisfaction assessment were to be performed.

Week 8 Visit (Visit 6)

Body weight/vital signs measurement, documentation of concomitant medicines, review of AEs, completion of diarrhea questionnaire if applicable, study drug accountability and dispensing, dispensing of rescue medicine as needed, IVRS compliance verification and reminder, EQ-5D, WPAI:C, and treatment satisfaction assessment were to be performed.

End of Treatment Period Visit (Visit 7)

Patients who were randomized but did not complete the Treatment Period (withdraw consent or are discontinued before the Week 12 Visit), were to be considered treatment withdrawals and were to complete the EOT Visit. Any clinical findings obtained during the final examination or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, were to be followed until the condition returns to screening status, has resolved or stabilized, or can be explained as being unrelated to study drug. Physical exam, body weight/vital signs measurement, documentation of concomitant medicines, review of AEs, completion of diarrhea questionnaire if applicable, study drug accountability, collection of blood/urine samples, PAC-QOL, EQ-5D, WPAI:C, and treatment satisfaction assessment, and IVRS registration were to be performed.

5.3.1.6 Study Phases

Screening Period:

During the Screening Period, subject eligibility for entry into the Pretreatment Period was determined. Any over-the-counter or prescription laxatives, suppositories, or enemas used to treat CIC were not allowed during the calendar day before the Pretreatment Visit; whereas other prohibited medicines were not allowed during the 14 calendar days before the Pretreatment Visit. The end of the Screening Period coincided with the start of the Pretreatment Period.

Pretreatment Period: The Pretreatment Period was defined as the 14 to 21 calendar days immediately before the Randomization Visit. During this period, patients provided the following information through daily calls to an interactive voice response system (IVRS):

- Daily Bowel Habits and Daily Patient Symptom Severity Assessments
- Weekly Patient Assessment of Constipation Severity
- Weekly Patient Assessment of Degree of Relief of Constipation Symptoms
- Use of Per-protocol Rescue Medicine or Any Other Laxatives, Suppositories, or Enemas

Patients who satisfied all of the entry criteria entered the Treatment Period.

Eligibility criteria were as follows:

- < 3 complete SBMs (CSBMs are SBMs accompanied by patient self-reporting a feeling of complete evacuation) per week
- ≤ 6 SBMs per week
- compliant with IVRS completion (i.e., they provided adequate responses on at least 10 days).

Patients were excluded for any of the following reasons:

- loose (mushy) stools in the absence of any laxative, suppository, enema, or prohibited medicine for > 25% of their BMs during the 12 weeks before the Screening Visit
- met the Rome III criteria for irritable bowel syndrome
- Bristol Stool Form Scale (BSFS) score of 7 for any SBM or a BSFS score of 6 for more than 1 SBM
- used Rescue Medicine (bisacodyl tablet or suppository) or any other laxative, suppository, or enema, on the calendar day before or the calendar day of the start of the Treatment Period (i.e., the Randomization Visit).

The schedule of events for the prescreening and screening period is provided in Table 6 below.

Table 6 Schedule of Events – Prescreening and Screening Periods

	Screening Period (Up to 21 days)	Pretreatment Period (14 to 21 days)
Visit Name/Day →	Screening Visit (Day -42 to Day -15)	Pretreatment Visit (Day -21 to Day -14)
Visit Number →	Visit 1	Visit 2
Trial Procedure ↓		
Inclusion and Exclusion Criteria Verification	X	X
Signature of ICF	X	
Medical History	X	
Physical Examination^b	X	
Body Weight and Height^c	X	X
Seated Vital Signs^d	X	X
Prior and Concomitant Medicines^e	X	X
Clinical Laboratory Tests^f	X	
Pregnancy Test	X	
Laxative/Suppository/Enema/Washout Instructions^h	X	
AE Evaluationsⁱ		X
IVRS Training or IVRS Compliance Verification and Reminder^k		X
Rescue Medicine Dispensed^l		X

Source: Reviewer's Table, modified from Applicant's Schedule of Events, CSR, p. 2196.

b. A physical examination included the following: general appearance, HEENT (head, ears, eyes, nose, and throat), neck, cardiovascular, thorax/lungs, breasts, abdomen, rectal, genitourinary, musculoskeletal, lymph nodes, skin, neurologic, and mental status. A rectal examination was performed during the Screening Period on all patients who did not require a colonoscopy. After the Screening Period, the rectal examination was optional and performed at the discretion of the investigator. Breast and genitourinary examinations were optional at the discretion of the investigator.

c. Height was measured only at the Screening Visit.

d. Vital signs were obtained in the seated position and included oral temperature, respiratory rate, blood pressure, and pulse.

e. At the Screening Visit, only information related to concomitant medicine that patients were taking on the day of the visit was captured.

f. Chemistry, CBC, and urine drug screen. The urine drug screen was performed at the Screening Visit only.

h. Trial coordinator instructed patients about the use of laxatives, suppositories, and enemas.

i. All AEs occurring after the patient signed the ICF were captured.

k. At the Pretreatment Visit, the trial coordinator instructed the patient about the use of the IVRS. At subsequent visits, the trial coordinator accessed the IVRS to verify patient compliance with the daily IVRS call requirement. After determining the patient's compliance, the trial coordinator reminded the patient to call the IVRS daily.

l. Rescue Medicine (oral bisacodyl or bisacodyl suppositories) was supplied to patients at the Pretreatment Visit and, if needed, at subsequent visits.

Treatment Period: The Treatment Period began with randomization and lasted for 12 weeks. Patients were stratified by baseline SBM frequency (i.e., those with > 1 SBM/week and those with \leq 1 SBM/week) and were randomized to treatment with linaclotide 72 ug, linaclotide 145 ug, or placebo (1:1:1). Study drug was taken once daily in the morning, at least 30 minutes before breakfast. Patients continued to call the IVRS to provide their daily assessments (Daily Bowel Habit Assessments and Daily Patient Symptom Severity Assessments), weekly assessments (Weekly Patient Assessment of Constipation Severity and Weekly Patient Assessment of Degree of Relief of Constipation Symptoms), and Use of Per-protocol Rescue Medicine or Any Other Laxatives, Suppositories, or Enemas. Quality-of-life and patient-outcome assessments were performed at trial visits throughout the Treatment Period. The schedule of events for the Treatment Period is provided in Table 7.

Table 7 Schedule of Events - Treatment Period

	<i>Treatment Period (12 weeks)</i>				
<i>Visit Days →</i>	<i>Randomization Visit (Day 1)</i>	<i>Week 2 Visit (Day 15 ± 3)</i>	<i>Week 4 Visit (Day 29 ± 3)</i>	<i>Week 8 Visit (Day 57 ± 3)</i>	<i>Week 12/End of Treatment Visit (n) (Day 85 + 3)</i>
<i>Visit Numbers →</i>	<i>Visit 3</i>	<i>Visit 4</i>	<i>Visit 5</i>	<i>Visit 6</i>	<i>Visit 7</i>
<i>Trial Procedure ↓</i>					
Inclusion and Exclusion Criteria Verification	X				
IVRS Registration	X				X
Medical History					
Physical Examination					X
Body Weight and Height^a	X	X	X	X	X
Seated Vital Signs^b	X	X	X	X	X
Prior and Concomitant Medicines	X	X	X	X	X
Clinical Laboratory Tests^c	X				X
Pregnancy Test	X				X
Laxative/Suppository/Enema/ Washout Instructions					
AE Evaluations	X	X	X	X	X
Diarrhea Questionnaire^d		X	X	X	X
Rescue Medicine Dispensed^e	X	X	X	X	
SBM Baseline Frequency Recall Question	X				
PAC-QOL	X		X		X
EQ-5D	X		X	X	X
WPAI:C	X		X	X	X
Study Drug Dispensed	X		X	X	

Source: Reviewer's Table, modified from Applicant's Schedule of Events, CSR, p. 2196.

^a Height is measured only at the Screening Visit.

^b Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse. At the Screening Visit, only information related to concomitant medicine that patients are taking on the day of the visit will be captured.

^c Chemistry, CBC, and urine drug screen. The urine drug screen will be performed at the Screening Visit only.

^d Patients who complain of diarrhea (or an AE that could be considered diarrhea) will complete the diarrhea questionnaire.

^e Rescue Medicine (oral bisacodyl or bisacodyl suppositories) will be supplied to patients at the Pretreatment Visit and, if needed, at subsequent visits.

5.3.1.7 Control Procedures

Randomization: A list of patient randomization codes was generated by Statistical Programming at Forest Research Institute, Inc., and implemented by the IVRS vendor (an electronic version was stored on a secure server). Patients were randomly assigned 1:1:1 to 1 of the 3 treatment groups.

Placebo Control:

This was a placebo-controlled trial. Placebo capsules were supplied as matching investigative drug, administered once daily (in the morning at least 30 minutes before breakfast).

Blinding:

This was a double-blind trial. Should a medical emergency occur, the blind could be broken. If the blind was broken, the trial center notified the Ironwood contact immediately. An explanation for breaking the blind was recorded on the relevant eCRF. Breaking the code at the trial center disqualified the patient from further participation in the trial.

Data Management:

Study data were entered from the eCRFs into an electronic data capture (EDC) system. The investigator and his/her staff were responsible for reviewing eCRFs, resolving data queries generated by the site monitor via the system, providing missing or corrected data, approving all changes performed on his/her data, and endorsing the patient data within the EDC system. This approval method included applying an electronic signature, which was a uniquely assigned username and password that together represented a traditional handwritten signature.

5.3.1.8 Outcome Measurements: Primary Endpoint

The primary endpoint was a 12-week Complete Spontaneous Bowel Movement (CSBM) Overall Responder defined as follows:

- A 12-week CSBM Overall Responder was a patient who was a CSBM Weekly Responder for at least 9 of the 12 weeks of the Treatment Period.

- A CSBM Weekly Responder for a Treatment Period week was a patient who had a CSBM weekly frequency rate that was 3 or greater and increased by 1 or more from baseline based on a minimum of 4 complete IVRS calls for that week. If a patient did not have at least 4 complete IVRS calls for a particular Treatment Period week, the patient was not considered a CSBM Weekly Responder for that week.
- A 12-week CSBM Overall Sustained Responder was a patient who met the 12-week CSBM Overall Responder criteria as defined above, and additionally was a CSBM weekly responder for ≥ 3 of the last 4 weeks of the Treatment Period.

Reviewer comments: The above responder definitions are consistent with what DGIEP finds acceptable for CIC. However, durability of response (12-week CSBM Overall Sustained Responder) was evaluated as an additional efficacy parameter in a pre-specified sensitivity analysis, rather than as part of the primary endpoint as recommended by FDA. Per the Applicant, the efficacy data analyses used an observed-cases approach. Effectively, this means that analyses will assume that no rescue medicine use or BMs occurred during missing data days.

For the primary efficacy assessment, the patient called into the Interactive Voice Response System (IVRS) each day of the Pretreatment and Treatment Periods, and provided the number of BMs he or she had since the previous day's call. Patient assessment of stool consistency was collected by daily IVRS calls. For each BM, stool consistency was assessed by the patient using the Bristol Stool Form Scale (BSFS). The 7-point ordinal BSFS scale is provided below:

"Please describe the consistency of the bowel movement using the following scale where:"

- 1=Separate hard lumps like nuts (difficult to pass)
- 2=Sausage shaped but lumpy
- 3=Like a sausage but with cracks on surface
- 4=Like a sausage or snake, smooth and soft
- 5=Soft blobs with clear-cut edges (passed easily)
- 6=Fluffy pieces with ragged edges, mushy stool
- 7=Watery, no solid pieces (entirely liquid)

For each BM, the patient also provided the day the BM occurred and if the BM was associated with a sense of complete evacuation. The patient was asked if he or she took any medicines to treat their constipation since the previous day's call. For each type of Rescue Medicine taken (e.g., oral bisacodyl, bisacodyl suppository) or other laxatives, suppositories, or enemas, the patient was asked to provide the day it was taken.

- The information that determined whether a BM was a CSBM was based on the following:

- The day of the BM - “How many bowel movements did you have since yesterday’s call at <IVRS inserts time when this question was answered yesterday>?” “Was this bowel movement today, or yesterday?” 1=Today, 2=Yesterday. “Did this bowel movement occur less than 24 hours after you first took study medication?” 1=Yes, 2=No
- Whether the BM was associated with a sense of complete evacuation was assessed by the patient answering the following IVRS question for each BM - “Did you feel like you completely emptied your bowels?” 1=Yes, 2=No
- Day of any Rescue Medicine Use - “Have you taken any laxatives, suppositories or enemas since yesterday’s call at <IVRS insert time when yesterday’s call was completed>?” 1=Yes, 2=No “Was this rescue medication use today, yesterday, or both today and yesterday?” 1=Today, 2=Yesterday, 3=Both Today and Yesterday

A 12-week CSBM Sustained Responder was assessed as a pre-specified sensitivity analysis of the primary endpoint, and was defined as a patient who was a CSBM Weekly Responder for at least 9 of the 12 weeks and at least 3 of the last 4 weeks of the Treatment Period.

5.3.1.9 Outcome Measurements: Secondary Endpoints

In addition to the primary endpoint, the applicant also included the following pre-specified (adjusted for multiplicity) secondary endpoints:

- Change from baseline in 12-week CSBM Frequency Rate
- Change from baseline in 12-week SBM Frequency Rate
- Change from baseline in 12-week Stool Consistency
- Change from baseline in 12-week Straining
- 12 week CSBM Overall Responder within the Baseline SBM Weekly Frequency > 1 Stratum
- Month 1 CSBM Responder
- Month 2 CSBM Responder
- Month 3 CSBM Responder
- Change from baseline in 12-week Abdominal Bloating
- Change from baseline in 12-week Abdominal Discomfort

The following efficacy assessments were used in determining the secondary efficacy parameters:

Spontaneous Bowel Movement:

The SBM assessment comprised the IVRS information that determined whether a BM was an SBM as follows:

- The day of the BM
- Day of any Rescue Medicine Use

Stool Consistency (Bristol Stool Form Scale):

Patient assessment of stool consistency was collected by daily IVRS calls. For each BM, stool consistency was assessed by the patient using the BSFS.

Straining:

Patient assessment of straining was collected daily by IVRS calls. For each BM, degree of straining was assessed by the patient using the following 5-point ordinal scale:

“How much did you strain during the bowel movement?”

- 1=Not at all
- 2=A little bit
- 3=A moderate amount
- 4=A great deal
- 5=An extreme amount

Daily Patient Assessment of Abdominal Discomfort:

Patient assessment of Abdominal Discomfort was collected daily by IVRS calls. The rating of abdominal discomfort during the previous 24 hours on an 11-point NRS was provided by the patient answering the following question:

“How would you rate your abdominal discomfort over the last 24 hours? Enter a number from 0 to 10, where 0 represents no abdominal discomfort and 10 represents very severe abdominal discomfort.”

Daily Patient Assessment of Abdominal Bloating:

Patient assessment of abdominal bloating was collected daily by IVRS calls. The rating of bloating during the previous 24 hours on an 11-point NRS was provided by the patient answering the following question:

“How would you rate your abdominal bloating over the last 24 hours? Enter a number from 0 to 10, where 0 represents no bloating and 10 represents very severe bloating.”

5.3.1.10 Statistical Information

The reader is referred to Dr. Shahla Farr’s statistical review for detailed information of the Applicant’s statistical analysis.

The Applicant calculated a sample size of 400 patients per treatment group, which was considered by the Applicant as adequate for 93% power to detect a difference between

linaclotide 72 ug and placebo in 12-week CSBM Overall Responder rate at a 2-sided significance level of 0.05 using a Fisher's Exact test. The primary analysis set for all efficacy analyses was the Intention-to-Treat population, defined as all randomized patients who received at least one dose of double-blind study drug.

The primary efficacy analysis was conducted by comparing the proportion of responders in the linaclotide 72 ug group with the proportion in the placebo group using a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by baseline SBM (weekly frequency > 1 versus ≤ 1) and geographic region. The 12-week CSBM Sustained Responder rates were compared between the linaclotide 72 ug group and the placebo group, and the analysis was conducted in the same manner as the primary efficacy analysis, by employing a 2-sided CMH test controlled for baseline SBM frequency and geographical region.

Controlling for Multiplicity: The overall family-wise Type I error rate for the comparisons of the linaclotide 72 ug dose versus placebo for the primary and the secondary efficacy parameters was controlled at the $\alpha = 0.05$ level by employing a 5-step serial gate-keeping MCP. Following this MCP, if the primary inference between the placebo group and the linaclotide 72 ug group in the overall patient population reached statistical significance ($\alpha = 0.05$) then the linaclotide 72 ug dose was considered efficacious and the MCP moved to the next step; otherwise, testing of the 72 ug dose was stopped.

Missing Data Handling: The potential impact of missing IVRS data related to the primary efficacy parameter on the estimates of treatment effect was assessed using alternative statistical methods [Last Observation Carried Forward (LOCF), Multiple Imputation (MI)]. The same CMH test used for the primary efficacy analysis was applied in these sensitivity analyses.

5.3.1.11 Protocol Amendments

The original protocol was dated 8/15/14. One protocol amendment was issued during the trial, and included the following modifications:

- The 4-step serial gate-keeping procedure established to control for multiplicity was modified to a 5-step serial gate-keeping MCP. The following new secondary efficacy parameters were added and were evaluated under the MCP:
 - 12 week CSBM Overall Responder within the Baseline SBM Weekly Frequency > 1 Stratum
 - Month 1 CSBM Responder
 - Month 2 CSBM Responder
 - Month 3 CSBM Responder
- The 12-week CSBM Sustained Responder and 6/12 Week CSBM Responder were removed from the list of planned additional efficacy parameters, and the following new additional efficacy parameters were added:

- 12-week CSBM Overall Responder in patients with ≤ 1 SBM/week at baseline
- Change from baseline in 12-week CSBM frequency rate by baseline SBM stratum
- Change from baseline in 12-week SBM frequency rate by baseline SBM stratum
- Change from baseline in 12-week Stool Consistency by baseline SBM stratum
- Change from baseline in 12-week Straining by baseline SBM stratum

The 12-week CSBM Overall Sustained Responder was evaluated as a sensitivity analysis of the primary efficacy parameter.

- The SBM baseline frequency recall question was added to the planned Health Outcome Assessments. Recall question results were tabulated against the SBM frequency total as reported in the daily diary during the last week of the Pretreatment Period
- Sensitivity analyses including, but not limited to, a multiple imputation approach, an LOCF approach, and ranked analyses were applied to the primary and secondary efficacy parameters. Further sensitivity analyses were performed employing a modified responder definition that emphasized the end of treatment (namely, 12-week CSBM Sustained Responder, defined as a patient who is a CSBM Weekly Responder for at least 9 of the 12 weeks and at least 3 of the last 4 weeks of the Treatment Period).

5.3.1.12 Withdrawal Criteria

Patients could be discontinued from the trial for the following reasons:

- Failure to meet Inclusion/Exclusion Criteria
- Adverse Event
- Insufficient therapeutic response (lack of efficacy)
- Protocol violation, including lack of compliance
- Withdrawal of consent
- Lost to follow-up (every effort must have been made to contact the patient; a certified letter must have been sent)
- Trial termination by Sponsor
- Other reasons, such as administrative reasons or pregnancy

Any patient who withdrew because of an AE was followed until the AE resolved, stabilized, or could be explained as being unrelated to study drug.

5.3.2 Protocol Summary, MCP-103-201

Title: A Randomized, Multicenter, Double-blind, Placebo-controlled, Dose-range-finding, Parallel-group, Phase 2 Trial of Oral Linaclotide Acetate Administered to Patients with Chronic Idiopathic Constipation

A brief synopsis of this study is discussed below, and the differences between this supportive phase 2 trial and the confirmatory phase 3 trial are highlighted.

Study MCP-103-201 was a 4-week, randomized, double-blind, placebo-controlled, dose-finding trial in patients with chronic constipation. The study evaluated 72ug, 145ug, 290ug, and 579ug doses of linaclotide and placebo. Subjects were enrolled if they met Rome II criteria for CIC. Four distinct periods were included: a screening period (Day -42 to -15; including drug washout), pre-treatment period (Day -14 to Day -1; includes baseline bowel habit, daily patient symptoms severity, and weekly patient global assessments), treatment period (Day 1 to Day 28; daily dosing of treatments; includes baseline bowel habit, daily patient symptoms severity, and weekly patient global assessments and rescue medication details) and post-treatment period (Day 29- Day 43; Daily Bowel Habits, Daily Patient Symptom Severity Assessments, Weekly Patient Global Assessments, and per-protocol rescue medication use).

The primary efficacy parameter was:

- change from baseline in the overall weekly SBM Frequency Rate during Weeks 1 through 4 of the Treatment Period.

The secondary efficacy parameters were:

- SBM Overall 75% Responder
- CSBM Overall 75% Responder
- change from baseline in the overall weekly CSBM Frequency Rate
- change from baseline in overall stool consistency, and change from baseline in overall straining score

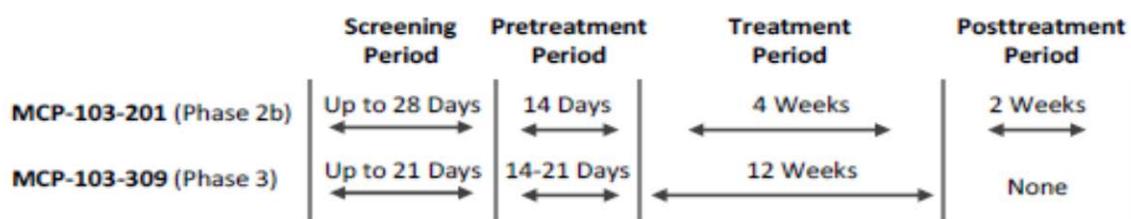
Changes from baseline in abdominal discomfort and abdominal bloating were also assessed as additional efficacy parameters. The primary and secondary efficacy analyses were based on the Evaluable Population (patients in the ITT Population who completed at least 4 days of dosing and IVRS questions in each of the 4 weeks of the Treatment Period and who had no major protocol violations during the Pretreatment or Treatment Periods).

The study designs for MCP-103-201 and MCP-103-309 were similar in that they both included a Screening Period to establish eligibility for study entry, a Pretreatment Period to establish baseline values, and a Treatment Period to assess the effects of blinded dosing compared with placebo. The Phase 2b trial also had a Posttreatment Period of observation following dosing that lasted 2 weeks.

The main difference between the two trials was the length of the Treatment Period: MCP-103-201 had a 4-week Treatment Period whereas MCP-103-309 had a 12-week Treatment Period. Therefore, responder parameters were also defined differently: MCP-103-201 defined a CSBM 75% Responder as a patient who was a CSBM Weekly Responder for ≥ 3 of the 4 Treatment Period weeks and MCP-103-309 defined a 12-week CSBM Overall Responder as a patient who was a CSBM Weekly Responder for ≥ 9 of the 12 weeks of the Treatment Period.

The study designs for MCP-103-201 and MCP-103-309 are presented in Figure 2.

Figure 2 Study Designs for MCP-103-201 and MCP-103-309



Source: Applicant's Figure 1-1, Summary of Clinical Efficacy, pg.13.

In addition, the phase 2b trial MCP-103-201 used Rome II criteria for eligibility, whereas the phase 3 trial MCP-103-309 used Rome III criteria for eligibility. The principal difference between Rome II and Rome III criteria is the time frame of the symptom history considered for diagnosis (12 months prior to diagnosis for Rome II vs. 3 months prior to diagnosis for Rome III). The Applicant provided literature support¹⁰ of an overall diagnostic agreement rate of 96% between Rome II and Rome III criteria in the diagnosis of functional constipation within a population of Chinese patients, and therefore concluded that the difference in time frame of symptoms prior to diagnosis was not expected to result in meaningful differences between study populations.

There were also minor changes with respect to rescue and concomitant medications, and are outlined below:

- **Provision of Rescue Medication:** During MCP-103-201, patients were instructed to contact the Investigator to obtain pre-defined rescue medication (oral bisacodyl, Fleet® enema, and bisacodyl suppository) if they experienced severe constipation. During MCP-103-309, a supply of rescue medication (bisacodyl tablet or suppository) was dispensed to patients at the Pretreatment Visit and, if necessary, at subsequent visits following randomization.

¹⁰ Xin HW, F. X. Diagnosis of functional constipation: Agreement between Rome III and Rome II criteria and evaluation for the practicality. J Dig Dis. 2014 Jun;15(6):314-20.

- **Use of Laxative, Suppository, or Enemas During the Pretreatment Period:** In MCP-103-201, patients were not eligible for randomization if they reported laxative, suppository, or enema use for > 2 days during the Pretreatment Period. In MCP-103-309, patients were not eligible for randomization if they reported laxative, suppository, or enema use on the calendar day before or the calendar day of the Randomization Visit.
- **Concomitant Medications:** During MCP-103-201, antihistamines (except loratadine and fexofenadine) were not permitted, and there were no restrictions with respect to proton pump inhibitors and glucocorticoids. During MCP-103-309, there were no restrictions with respect to antihistamines; patients taking proton pump inhibitors were required to be on a stable dose for 30 days before the Screening Visit with no plan to change the dose; and oral and parenteral glucocorticoids were excluded, except for a single, short course of oral glucocorticoids or a single injection of parenteral glucocorticoids.

Reviewer comments: In this reviewer's opinion, the populations studied in both trials were generally similar and the differences would be not be expected to significantly impact the characteristics of the subjects enrolled.

6 Review of Efficacy

Efficacy Summary

Clinical trial MCP-103-309 provided statistically persuasive evidence to support that linaclotide 72ug once daily is effective for the treatment of CIC in adults. This clinical trial was a 12-week, multi-center, randomized, DB, placebo-controlled, parallel-group phase 3 trial in subjects with CIC to evaluate the efficacy and safety of linaclotide 72 ug administered once daily to patients with CIC. The linaclotide 145 ug dose, already approved for this indication, was included in this trial as an established positive control. 1223 subjects were randomized 1:1:1 to receive placebo, 72ug linaclotide, or 145ug linaclotide at 105 clinical sites in the US. The treatment arms were generally well balanced with regards to demographics and baseline disease characteristics.

The pre-specified primary efficacy parameter was 12-week CSBM Overall Responder which required patients to be weekly responders for at least 9 of 12 weeks. The proportion of CSBM Overall Responders over weeks 1 – 12 was significantly higher in patients receiving linaclotide 72ug compared to placebo (13.4% vs 4.7%, $p < 0.0001$).

The sustainability of the 12-week CSBM Overall response was evaluated in a pre-specified sensitivity analysis and required patients to be weekly responders for at least 9 of the 12 weeks, including at least 3 of the last 4. The proportion of CSBM Sustained Responders over weeks 1-12 was significantly higher in patients receiving linaclotide 72ug compared to placebo (12.4% vs 4.7%, $p = 0.0001$).

In addition to the primary endpoint, the applicant also included a number of pre-specified secondary endpoints which were adjusted for multiplicity.

The secondary endpoint findings generally appear to be supportive of the primary endpoint results. As reported by the Sponsor, linaclotide 72 ug met 9 of 10 secondary trial efficacy parameters, and demonstrated statistically significantly higher responder rates versus placebo for the 4 secondary efficacy parameters with responder endpoints, including the 12-week CSBM Overall Responder in a subpopulation of patients who reported > 1 SBM/week during Pretreatment, and the Monthly CSBM Responder Analyses, which required patients to meet the CSBM weekly responder criteria for ≥ 3 of the 4 weeks of Months 1, 2, and 3 of the Treatment Period. Five of the 6 secondary change-from-baseline parameters were also reported to be statistically significant for linaclotide 72 ug versus placebo, including 12-week change in CSBM and SBM frequency, stool consistency (BSFS score), straining, and abdominal bloating. Numerical improvements in abdominal discomfort were obtained for the linaclotide 72 ug dose compared with placebo.

The linaclotide 145 ug dose that is approved for this indication was included in this trial as an established positive control. Among the primary and secondary efficacy parameters with responder endpoints, the results with the linaclotide 72 ug dose were reported to be similar to the results obtained with the 145 ug dose. For the secondary change-from-baseline parameters, the results with linaclotide 72 ug were numerically lower than the results with linaclotide 145 ug; however, the study was not designed to compare the two doses.

Supportive efficacy data from a phase 2b trial, MCP-103-201, was also provided for the 72ug dose. This phase 2 trial was reviewed as part of the original NDA submission; for details the reader is referred to the clinical review by Dr. Wynn, as well as the clinical pharmacology review by Dr. Sandhya Apparaju dated 4/6/2012. The primary efficacy parameter was the change from baseline in the overall weekly SBM Frequency Rate during Weeks 1 through 4 of the Treatment Period. The secondary efficacy parameters were SBM Overall 75% Responder, CSBM Overall 75% Responder, change from baseline in the overall weekly CSBM Frequency Rate, change from baseline in overall Stool Consistency, and change from baseline in overall Straining score. Linaclotide daily doses of 72ug, 145ug, 290ug, and 579ug were all reported to improve frequency of SBMs and CSBMs, stool consistency, abdominal discomfort, and abdominal bloating compared with placebo. Across the 4 doses, there was evidence of a dose response for the primary efficacy parameter (SBM Frequency Rate) as well as the other bowel symptoms. In addition, there were more responders at the 2 higher doses (290 and 579 ug) compared with the 2 lower doses (72 and 145 ug). Linaclotide 72 and 145 ug demonstrated similar efficacy for CSBM 75% Responder, SBM and CSBM frequency rates, stool consistency, and straining.

Reviewer comments: Data from MCP-103-201 appear to support that the 72ug dose demonstrates similar efficacy to the approved 145ug dose. See Section 6.1.8

Analysis of Clinical Information Relevant to Dosing Recommendations for further discussion of dose response.

The following sections present more detailed information on the efficacy results of MCP-103-309. High level results from MCP-103-201 are summarized as well.

6.1 Indication

The proposed indication is for adult patients with chronic idiopathic constipation (CIC).

6.1.1 Methods

The Sponsor submitted a 12-week, multi-center, randomized, DB, placebo-controlled, phase 3 trial in subjects with CIC (MCP-103-309) for this sNDA. The results from this trial are discussed in this review and the data was not pooled from previous efficacy trials. A total of 105 centers in the United States consented 1 or more patients and 99 centers randomized 1 or more patients. A total of 1223 subjects were randomized.

Subjects eligible to participate were those \geq 18-years of age who, at study entry, met modified Rome III criteria for CIC and did not meet the Rome III criteria for IBS, who had $<$ 3 complete spontaneous BMs (CSBMs) and \leq 6 SBMs per week, and did not report loose (mushy) or watery stools (Bristol Stool Form Scale [BSFS] score of 6 or 7) in the absence of any laxative, suppository, enema, or prohibited medicine for $>$ 25% of BMs during the 12 weeks before the Screening Visit. Please see Section 5.3 Discussion of Individual Studies/Clinical Trials for key inclusion and exclusion criteria. The primary efficacy endpoint for this trial was the proportion of subjects who were 12-week CSBM Overall Responders.

Analysis Populations:

A summary of the analysis populations follow, and is presented in Table 8.

Randomized Population: All patients in the Screened Population who were randomly assigned to a treatment group in the trial at the Randomization Visit.

The Intent-to-treat (ITT) Population: All randomized patients who received at least one dose of double-blind study drug. Patients were evaluated according to the treatment group they were assigned to at randomization. Efficacy analysis was based on the ITT Population.

Safety Population: All patients in the Randomized Population who received at

least 1 dose of double-blind study drug (placebo, linaclotide 72 ug, or linaclotide 145 ug). Safety analysis was to be based on the Safety Population, in which patients were evaluated according to the treatment they actually received.

Table 8 Summary of Analysis Populations

Patient Population	Placebo	Linaclotide		Total
		72 ug	145 ug	
Randomized Population	401	411	411	1223
Safety Population	401	411	411	1223
ITT Population	401	411	411	1223
ITT Population by Geographic Region ^a :				
Southeast	247	254	243	744
West	60	57	65	182
Southwest	49	41	52	142
Northeast	25	36	31	92
Midwest	20	23	20	63

Data source: Section 14, Table 14.1.1

a. Geographic regions are defined in Section 16.3 of the SAP.

Source: Applicant's Table from CSR, pg. 92.

***Reviewer comments:** A majority of patients were enrolled in the Southeast region. The Applicant reports that across the 5 geographic regions, there were no differences observed in demographics, patient baseline characteristics, or study conduct (including protocol deviations, IVRS compliance, and dosing compliance) that were considered likely to have impacted the overall trial conclusions. Further discussion of efficacy across geographic regions may be found in Section 3.2 Compliance with Good Clinical Practices.*

6.1.2 Demographics

Demographics characteristics are presented in Table 9. The majority of patients were Caucasian (71.0%) and female (77.0%). Hispanic or Latino ethnicity was reported by 43.2% of patients. Mean patient age for all patients was 46.0 years; means for individual treatment groups were 45.2 years for the placebo group, 45.8 years for the linaclotide 72 ug group, and 46.8 years for the linaclotide 145 ug group. Patients ≥ 65 years of age composed 9.6% of the Safety/ITT Population; Black or African American patients composed 23.6%.

Table 9 Demographic and Baseline Characteristics (Safety Population)

Demographic Characteristic	Placebo (N=401)	Linaclotide		Total (N=1223)
		72 ug (N=411)	145 ug (N=411)	
Age, years				
Mean (SD)	45.2 (14.7)	45.8 (14.3)	46.8 (14.0)	46.0 (14.3)
Median (Min, Max)	46.0 (18, 83)	46.0 (18, 90)	47.0 (18, 86)	46.0 (18, 90)
Age, n (%)				
18 to < 40 years	142 (35.4)	140 (34.1)	128 (31.1)	410 (33.5)
40 to < 65	220 (54.9)	235 (57.2)	240 (58.4)	695 (56.8)
≥ 65 years	39 (9.7)	36 (8.8)	43 (10.5)	118 (9.6)
Gender, n (%)				
Female	316 (78.8)	312 (75.9)	314 (76.4)	942 (77.0)
Male	85 (21.2)	99 (24.1)	97 (23.6)	281 (23.0)
Race, n (%)				
Caucasian	276 (68.8)	298 (72.5)	294 (71.5)	868 (71.0)
Non-Caucasian	125 (31.2)	113 (27.5)	117 (28.5)	355 (29.0)
Black/African American	102 (25.4)	93 (22.6)	94 (22.9)	289 (23.6)
Asian	18 (4.5)	14 (3.4)	16 (3.9)	48 (3.9)
Other	5 (1.2)	6 (1.5)	7 (1.7)	18 (1.5)
Ethnicity, n (%)				
Hispanic or Latino	175 (43.6)	178 (43.3)	175 (42.6)	528 (43.2)
Not Hispanic or Latino	226 (56.4)	233 (56.7)	236 (57.4)	695 (56.8)
Baseline SBM Stratum, n (%)				
≤ 1 SBM/week	175 (43.6)	167 (40.6)	176 (42.8)	518 (42.4)
> 1 SBM/week	226 (56.4)	244 (59.4)	235 (57.2)	705 (57.6)
Weight, kg				
Mean (SD)	80.3 (19.7)	79.7 (18.1)	80.1 (18.8)	80.0 (18.8)
Median (Min, Max)	78.8 (44, 193)	78.5 (40, 141)	78.0 (45, 158)	78.3 (40, 193)
Height, cm				
Mean (SD)	165.3 (9.0)	165.8 (9.0)	165.3 (9.5)	165.5 (9.2)
Median (Min, Max)	165.0 (135, 205)	165.1 (147, 196)	165.0 (142, 201)	165.1 (135, 205)
BMI, kg/m²				
Mean (SD)	29.3 (6.5)	28.9 (6.0)	29.3 (6.2)	29.2 (6.2)
Median (Min, Max)	28.6 (16, 59)	28.0 (15, 64)	28.2 (17, 56)	28.2 (15, 64)

Data source: Section 14, [Table 14.2.1](#)

Age is calculated up to the informed consent date.

SD = standard deviation; Min = minimum; Max = maximum; BMI = body mass index, defined as weight in kg divided by height in m².

Source: Applicant's Table 8, CSR, pg. 93-94.

Reviewer comments: The placebo and linaclotide arms within the trial were generally well matched with regard to baseline demographics and other baseline characteristics. Gender groups were balanced across all arms of the trial, however the number of randomized subjects who were male was substantially less than female subjects (approximately 1/3 of randomized subjects were male), which is reflective of the demographics affected by the disease in the general population¹¹. Based on the known natural history of CIC, the trial population was similar to the general population. No significant differences in efficacy findings would be expected based on these demographic differences. However, the demographic subsets of subjects were limited by the inadequate percentage of male subjects. This is discussed further in Section 6.1.7 Subpopulations.

6.1.3 Subject Disposition

A total of 2244 patients were screened; 1223 successfully completed the Screening and Pretreatment Periods, and were randomized to treatment. Of the 1223 randomized patients, 1078 (88.1%) completed the Treatment Period. The ITT Population included 1223 patients who received ≥ 1 dose of double blind study drug during the Treatment Period (411 in the 72 ug group, 411, in the 145 ug group, and 401 in the placebo group). The Safety Population (N=1223) was identical to the ITT Population.

Of the 2244 patients that were screened, 1021 were not randomized: 478 patients were screen failures (patients who sign an ICF but did not qualify for inclusion into the study based on their Screening evaluations) and 543 patients were pretreatment failures (patients who signed an ICF, entered the pretreatment period but were not randomized into the study.). The primary reason for screen and pretreatment failure among these subjects was not meeting inclusion/exclusion criteria (804 subjects, 36%). Reasons for screen and pretreatment failure for the screened population are listed in Table 10.

¹¹ Sonnenberg A, K. T. (1989 Jan.). Epidemiology of constipation in the United States. Dis Colon Rectum. , 32(1):1-8.

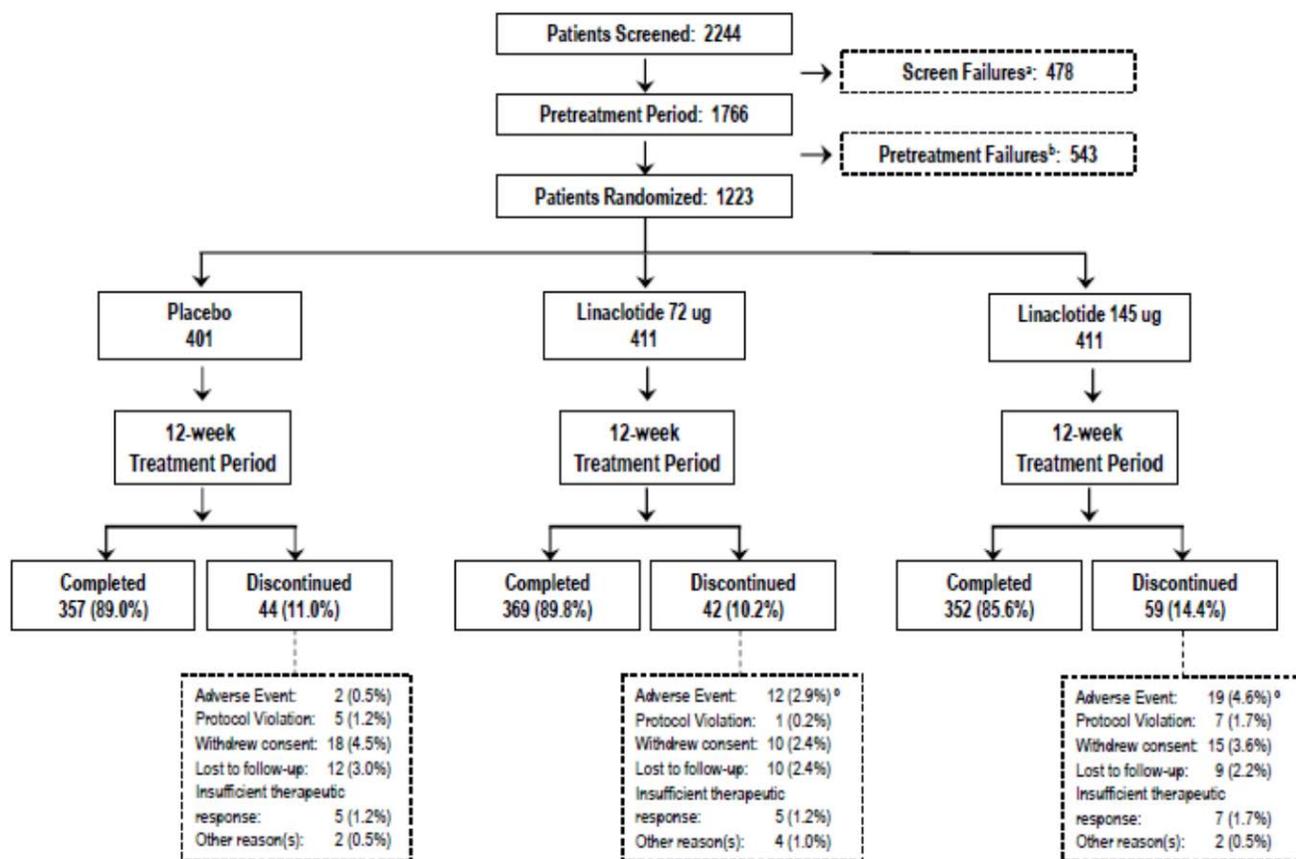
Table 10 Reasons for Screen and Pretreatment Failure

	Total (N=2244) n (%)
Screen Failures	478 (21.3)
Reason for Screen Failure	
Patient did not meet Inclusion/Exclusion Criteria	346 (15.4)
Adverse Event	0
Protocol Violation	0
Withdrawal of Consent	77 (3.4)
Lost to Follow-Up	25 (1.1)
Other	30 (1.3)
Pretreatment Failures	543 (24.2)
Reason for Pretreatment Failure	
Patient did not meet Inclusion/Exclusion Criteria	458 (20.4)
Adverse Event	1 (0.0)
Protocol Violation	1 (0.0)
Withdrawal of Consent	47 (2.1)
Lost to Follow-Up	10 (0.4)
Other	26 (1.2)

Source: Applicant's Table 14.1.2, slightly modified by this reviewer, Applicant's CSR, pg. 170.

One hundred forty-five randomized subjects (12%) withdrew early from the treatment period. Reasons for early discontinuation from the trial are shown in Figure 3.

Figure 3 Subject Disposition (All Enrolled Subjects)



Source: Sponsor's Figure 2, reproduced from CSR, pg. 89.

Data source: Section 14, Tables 14.1.1, 14.1.2, and 14.1.3

a. Patients who signed an ICF but did not qualify for inclusion into the trial base on their Screening Visit

evaluations. Patients who were re-screened and failed the second time during the Screening Period were only counted once.

b. Patients who signed an ICF, entered the Pretreatment Period, but were not randomized into the trial. Patients who were re-screened and failed the second time during the Pretreatment Period were counted only in the pretreatment failure category. Patients who were re-screened and became randomized are not counted in either of the failure categories.

c. $p = 0.0123$ for the linaclotide 72 ug group and $p = 0.0002$ for the linaclotide 145 ug group versus placebo (from pairwise comparisons with the placebo group using the Fisher exact test). The p -values for all other comparisons were > 0.05 . (Section 14, Table 14.1.3).

Reviewer comments: *There was approximately a 10-14% dropout rate in each treatment arm. This is a lower rate of discontinuations than was seen in the phase 3 pivotal trials that supported original approval (13.2% in the placebo arm, 16.7% in the 145ug arm, and 18.2% in the 290ug arm). The number of discontinuations secondary to adverse events appears to be dose-dependent, with the greatest number of dropouts in the 145ug arm. [See Section 7.3.3 Dropouts and/or Discontinuations]. The numbers of subjects who were lost to follow up appear to be distributed evenly among treatment groups and would not be expected to impact efficacy analyses.*

On initial review of the Applicant's table detailing reasons for discontinuation, specific reasons that were lumped under the heading of "Other reason(s)" were not clear to this

reviewer. The specific reasons were located by this reviewer in the Applicant’s DS dataset and are outlined in Table 11.

Table 11 Reasons Classified as “Other reason(s)” of Subject Discontinuation

<i>“Other” Reason for Discontinuation</i>	<i>N (Placebo)</i>	<i>N (Linaclotide 72 ug)</i>	<i>N (Linaclotide 145 ug)</i>
Exclusionary medication	1	0	0
Unexpectedly had to go out of town	0	0	1
Patient’s schedule would not allow	0	1	0
Patient is moving out of state	0	1	0
Personal reasons	0	0	1
Subject attempting dual site enrollment	1	0	0
Transportation problem	0	1	0
Unable to come in for visits	0	1	0

Source: Reviewer’s table, modified from Applicant’s Table 14.1.3 MCP-103-309 CSR, and Applicant’s DS dataset.

Reviewer comments: None of the 8 subjects in the “Other” category were discontinued secondary to an AE. In addition, the numbers of subjects who were classified as “Other” are small, and would not be expected to impact efficacy analyses.

Table 12 summarizes baseline efficacy variables during the Pretreatment Period.

Table 12 Baseline Efficacy Variables (ITT Population)

Efficacy Parameter	Statistic	Placebo (N=401)	Linaclotide		Total (N=1223)
			72 ug (N=411)	145 ug (N=411)	
CSBM Weekly Rate	n	401	411	411	1223
	Mean (SD)	0.25 (0.48)	0.22 (0.52)	0.20 (0.44)	0.22 (0.48)
	Median	0.00	0.00	0.00	0.00
	Min, Max	0.0, 2.4	0.0, 2.9	0.0, 2.4	0.0, 2.9
SBM Weekly Rate	n	401	411	411	1223
	Mean (SD)	1.56 (1.15)	1.74 (1.42)	1.67 (1.38)	1.66 (1.33)
	Median	1.45	1.46	1.45	1.45
	Min, Max	0.0, 5.8	0.0, 6.3	0.0, 6.3	0.0, 6.3
Stool Consistency (BSFS) ^a	n	359	360	364	1083
	Mean (SD)	2.04 (1.02)	1.94 (0.93)	1.96 (0.94)	1.98 (0.96)
	Median	2.00	1.83	1.75	1.83
	Min, Max	1.0, 6.0	1.0, 6.0	1.0, 7.0	1.0, 7.0
Straining ^a	n	359	360	364	1083
	Mean (SD)	3.51 (0.88)	3.62 (0.86)	3.52 (0.82)	3.55 (0.85)
	Median	3.75	3.80	3.67	3.71
	Min, Max	1.0, 5.0	1.0, 5.0	1.0, 5.0	1.0, 5.0
Abdominal Discomfort	n	401	411	411	1223
	Mean (SD)	4.76 (2.56)	4.64 (2.74)	4.71 (2.66)	4.70 (2.65)
	Median	4.92	4.87	4.64	4.85
	Min, Max	0.0, 9.9	0.0, 10.0	0.0, 10.0	0.0, 10.0
Abdominal Bloating	n	401	411	411	1223
	Mean (SD)	5.29 (2.39)	5.24 (2.61)	5.30 (2.57)	5.27 (2.52)
	Median	5.40	5.43	5.33	5.40
	Min, Max	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0

Data source: Section 14, Table 14.2.4.1

Baseline efficacy values are derived from the IVRS daily diary data collected in the Pretreatment Period, specifically the period of time from 14 days before randomization up to the time of randomization.

SD = Standard Deviation, Min = Minimum, and Max = Maximum.

a. Patients who did not have an SBM at baseline had missing Stool Consistency and Straining baseline scores.

Source: Applicant's Table 9, CSR, pg. 95

Reviewer comments: The baseline constipation status among the treatment groups appears generally comparable. It should be noted that the baseline disease status (e.g., CSBM and SBM weekly rate) were compared by this reviewer to the population studied in the 2 pivotal trials leading to the approval of linaclotide 145 ug for this indication, and were similar to MCP-103-309.

Treatment and IVRS Compliance

Treatment compliance was calculated as (Total number of capsules taken) x 100/(Total number of capsules expected to be taken). The mean treatment compliance rates for the overall Treatment Period were >97% across treatment groups. Overall, the percentage of patients who were ≥ 80% IVRS compliant during the 2-week Pretreatment Period was >94%, and for the 12-week Treatment Period was >70%.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy parameter was 12-week CSBM Overall Responder. A 12-week CSBM Overall Responder was a patient who was a CSBM Weekly Responder for ≥ 9 of the 12 weeks of the Treatment Period. A CSBM Weekly Responder was a patient who had a CSBM weekly frequency rate that was 3 or greater and increased by 1 or more from baseline. The treatment difference between the placebo group and the linaclotide 72ug group on the 12-week CSBM Overall Responder rate was 8.7% ($p < 0.0001$). The linaclotide 145ug dose was included in the trial as an established positive control as it is the approved dose of linaclotide in CIC. The treatment difference between the placebo group and the linaclotide 145ug group was 7.7% ($p = 0.0001$).

The Applicant's prespecified analysis of the primary endpoint used a worst case method for handling missing data. Specifically, subjects with fewer than 4 complete IVRS calls during an analysis week was considered a nonresponder for that week. Per this analysis, significantly more linaclotide-treated subjects compared with placebo-treated subjects were Overall CSBM Responders for the 12 week Treatment Period. This response is presented by the Applicant in Table 13 and Figure 4.

Table 13 Primary Endpoint: 12-Week CSBM Overall Responders (ITT Population)

MCP Step Efficacy parameter	Placebo (N=401)	Linaclotide 72 ug (N=411)		MCP met?	
MCP Step 1 – Primary Efficacy Parameter (ITT Population)					
Responder	n/N (%)	n/N (%)	OR ^b (95% CI)	p-value ^b	Yes/No
12-week CSBM Overall ^{a,b,c}	19/401 (4.7)	55/411 (13.4)	3.03 (1.76, 5.20)	<0.0001	Yes

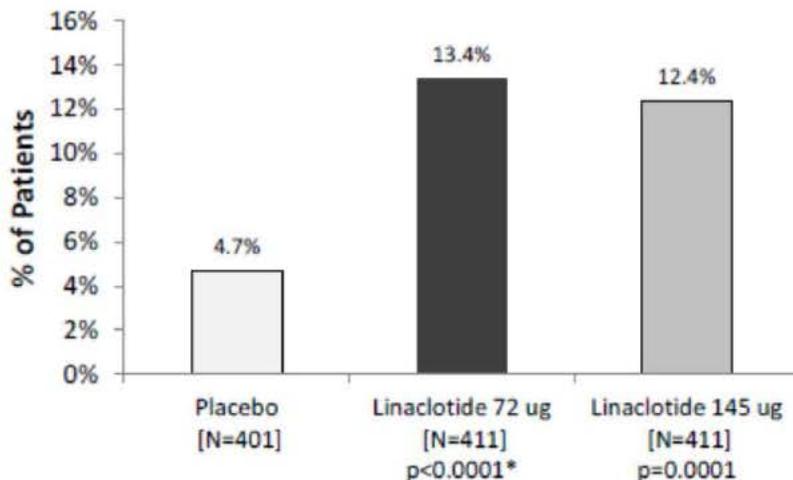
Source: Reviewer’s Table, modified from Applicant’s Table 11, CSR, page 98.

^a A 12-week CSBM Overall Responder is a patient who was a CSBM Weekly Responder for at least 9 of the 12 weeks of the Treatment Period. A CSBM Weekly Responder is a patient who had a CSBM weekly frequency rate that was 3 or greater and increased by 1 or more from baseline, and completed ≥4 IVRS calls for the specified week. A patient with fewer than 4 complete IVRS calls during an analysis week was not considered a responder for that week.

^b Odds ratio (95% CI) and p-values were obtained from the CMH tests controlling for baseline SBM stratum and geographic region.

^c Worst case: Subjects with fewer than 4 complete IVRS calls during an analysis week was considered a nonresponder for that week.

Figure 4 12-Week CSBM Overall Responder (ITT Population)



Data source: Section 14, Table 14.4.1.1A

P-values for each linaclotide dose versus placebo were obtained from the CMH tests controlling for baseline SBM stratum and geographic region.

* Statistically significant

Source: Applicant’s Figure 3, CSR, pg.101.

The primary efficacy analysis was conducted by comparing the proportion of responders in the linaclotide 72 ug group with the proportion in the placebo group using a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by baseline SBM stratum (weekly frequency > 1 versus ≤ 1) and geographic region. The number and percentage of responders in each group, the difference in responder rate and odds ratio comparing

the linaclotide 72 ug group and placebo group, the corresponding confidence intervals for each estimate, and the 2-sided p-value associated with the CMH test were presented. The overall family-wise Type I error rate for the comparisons of linaclotide 72 ug versus placebo for the primary and secondary efficacy parameters was controlled by employing a 5-step serial gate-keeping MCP ($\alpha = 0.05$). To evaluate the impact of missing data, 2 sensitivity analyses [Last Observation Carried Forward (LOCF) and multiple imputation (MI)] were also conducted. Under the LOCF approach, if a patient had < 4 complete IVRS calls for any of the 12 Treatment Period weeks, the patient's responder status for that week was imputed by the value of the patient's responder status from the previous week during the Treatment Period. Using the MI approach, the CSBM change-from-baseline rate during a Treatment Period week was treated as missing if a patient had < 4 complete IVRS calls during that week, and the missing data were assumed to follow a missing at random (MAR) pattern.

Reviewer comments: The Applicant's worst case analysis of the primary endpoint, which was the prespecified primary analysis, yields a treatment difference of 8.7% and a p-value of <0.0001. Although the treatment difference is somewhat lower than the effect size demonstrated in the trials conducted to support the approval of the 145ug dose of Linzess in CIC (16.9% and 9.9%), a statistically significant difference in the primary endpoint may be considered clinically meaningful by the Division if it is accompanied by some reduction in risk and/or improvement in tolerability. In addition, in this trial there was a treatment difference of 7.7% when comparing the 145 ug dose with placebo. Although it is unclear what contributed to the difference between effect sizes between MCP-103-309 and the pivotal studies supporting the approval of the 145ug dose, it appears that the 72ug dose was demonstrated to be effective by achieving its primary endpoint.

In order to ensure that the 12-week CSBM Overall Responder analysis represented adequate duration of response, secondary analyses of monthly CSBM responders and a sensitivity analysis employing a modified responder definition that emphasizes the end of treatment were also studied. A 12-week CSBM Sustained Responder was a patient who was a CSBM Weekly Responder for at least 9 of the 12 weeks and at least 3 of the last 4 weeks of the Treatment Period.

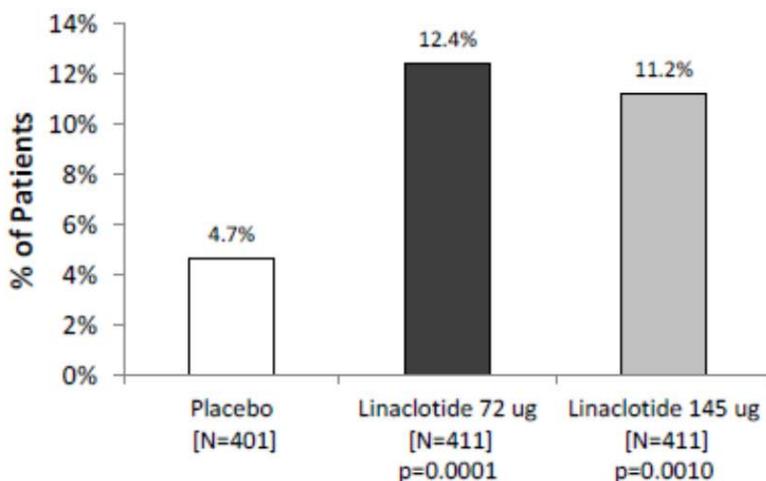
Reviewer comments: At the meeting that took place on September 9, 2014, the FDA recommended that the primary endpoint include an assessment of durability of response; the Applicant elected to maintain their original plan to use the original phase 3 primary endpoint as the primary endpoint to enable placing the results from the 72ug dose in context with results from the already approved dose appearing in the label. In order to ensure that the 12-week CSBM Overall Responder analysis represented adequate duration of response, a sensitivity analysis employing a modified responder definition (the FDA's recommended primary endpoint) was conducted, and is discussed further in Section 6.1.4.1 12-week CSBM Overall Sustained Responder. The recommended monthly responder analysis to assess the durability of response was

included as a prespecified secondary analysis, and is further discussed in Section 6.1.5 Analysis of Secondary Endpoints(s).

6.1.4.1 12-week CSBM Overall Sustained Responder

The sustainability of the 12-week CSBM Overall response was evaluated in a prespecified sensitivity analysis. The Applicant is seeking to include these findings in the drug labeling. A 12-week CSBM Sustained Responder is defined as a patient who is a CSBM Weekly Responder for at least 9 of the 12 weeks and at least 3 of the last 4 weeks of the Treatment Period. The linaclotide 72 ug group was reported to have a greater response rate (12.4%) compared with the placebo group (4.7%), for a treatment difference of 7.7%. The response rate for the linaclotide 145 ug group was slightly lower than the 72 ug dose group (11.2%), for a treatment difference of 6.5%. The results of the 12-week CSBM Overall Sustained Responder analysis are presented in Figure 5.

Figure 5 12-Week Overall Sustained Responder (ITT Population)



Data source: Section 14, [Table 14.4.1.1D](#)

P-values for each linaclotide dose versus placebo were obtained from the CMH tests controlling for baseline SBM stratum and geographic region.

Source: Applicant's Figure 4, CSR, pg. 102.

Reviewer comments: *The FDA-recommended primary endpoint includes an assessment of durability of response. The Applicant's primary endpoint did not assess durability as part of the primary endpoint, but addressed the Division's concern by prespecifying a sensitivity analysis that evaluated sustainability. This sensitivity analysis assessing 12-Week Overall Sustained Responders continues to show a higher response rate in the 72ug arm compared to placebo ($\Delta=7.7\%$, $p = 0.0001$).*

The results of each of the above sensitivity analyses appear to show no appreciable effect of missing data on the primary efficacy outcome as defined by the Applicant. The statistical reviewer also reanalyzed the data based on those subjects who completed the study, and the results were similar to that of the ITT population. Please see the Biostatistics review by Dr. Shahla Farr dated 11/10/2016.

Reviewer comments: *The magnitude of the linaclotide treatment effect was consistent despite the use of various methodologies for handling missing data. The results of the sensitivity analyses appeared to support the primary analysis.*

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant prespecified and adjusted for multiplicity 10 secondary efficacy parameters (6 change-from-baseline parameters and 4 responder parameters) :

- Change from baseline in 12-week CSBM Frequency Rate
- Change from baseline in 12-week SBM Frequency Rate
- Change from baseline in 12-week Stool Consistency
- Change from baseline in 12-week Straining
- 12 week CSBM Overall Responder within the Baseline SBM Weekly Frequency >1 Stratum
- Month 1 CSBM Responder
- Month 2 CSBM Responder
- Month 3 CSBM Responder
- Change from baseline in 12-week Abdominal Bloating
- Change from baseline in 12-week Abdominal Discomfort

The overall family-wise Type I error rate for the comparisons of linaclotide 72 ug versus placebo for the primary and secondary efficacy parameters was controlled by employing a 5-step serial gate-keeping MCP ($\alpha = 0.05$). Although all 10 secondary efficacy parameters were tested, each comparing the linaclotide 72 ug dose to placebo, the Applicant is not seeking to include these findings in the drug labeling. As such, the findings are briefly summarized below.

6.1.5.1 Change from baseline in 12-week CSBM Frequency Rate

A patient's 12-week CSBM frequency rate was the CSBM rate (CSBMs/week) calculated over the 12 weeks of the Treatment Period. The mean baseline values for CSBM frequency rates (CSBMs/week) were reported to be low for all 3 groups (0.25, 0.22, and 0.20 for the placebo, linaclotide 72 ug, and linaclotide 145 ug groups, respectively). The least squares (LS) mean change from baseline in 12-week CSBM Frequency Rate for the linaclotide 72 ug group (1.7 CSBMs) was reported to be greater than for placebo (0.9 CSBMs), ($p < 0.0001$). A higher increase from baseline (1.9 CSBMs) was noted for the linaclotide 145 ug group ($p < 0.0001$).

6.1.5.2 Change from baseline in 12-week SBM Frequency Rate

A patient's 12-week SBM frequency rate was the SBM rate (SBMs/week) calculated over the 12 weeks of the Treatment Period. As observed with CSBMs, the LS mean change from baseline in SBM frequency for the linaclotide 72 ug group (2.4 SBMs) was greater than placebo (1.3 SBMs); ($p < 0.0001$). The increase in SBMs for the linaclotide 145 ug group (2.6 SBMs) was again slightly greater than that for the 72 ug group ($p < 0.0001$).

6.1.5.3 Change from baseline in 12-week Stool Consistency

Stool consistency was measured daily using the 7-point BSFS. The patient's BSFS score for the Treatment Period was the average of the non-missing BSFS scores from the SBMs reported by the patient during the 12-week Treatment Period. If a patient had no SBMs at baseline, then the baseline Stool Consistency was missing and the patient was excluded from Stool Consistency analyses that involved change from baseline. The baseline BSFS scores were 2.0, 1.9, and 1.9 for the placebo, linaclotide 72 ug, and 145 ug groups, indicating lumpy, firm stool form. The LS mean changes from baseline in Stool Consistency for the linaclotide 72 ug group (1.7) was reported to be greater than placebo (1.1), ($p < 0.0001$). A similar level of change (1.8) was noted for the linaclotide 145 ug group ($p < 0.0001$). Over the 12-week Treatment Period, both linaclotide dose groups demonstrated mean BSFS scores approaching 4, indicating smooth, soft stool form that is within the normal range of 3 to 5.

6.1.5.4 Change from baseline in 12-week Straining

Straining was measured daily using a 5-point ordinal scale. The patient's straining score for the Treatment Period was the average of the non-missing straining scores from the SBMs reported by the patient during the 12-week Treatment Period. If a patient had no SBMs at baseline, then the baseline Straining was missing and the patient was excluded from Straining analyses that involved change from baseline. The LS mean change from baseline in Straining for the linaclotide 72 ug group (-1.1) demonstrated greater improvement (decrease) from baseline compared with placebo (-0.8), ($p < 0.0001$). A similar level of change (-1.2) was noted for the linaclotide 145 ug group ($p < 0.0001$).

Reviewer comments: Please note that the following comments are in reference to Sections 6.1.5.1 through 6.1.5.4: The change from baseline endpoints in CSBM frequency rate, SBM frequency rate, stool consistency, and straining demonstrate similar efficacy to the 145ug dose, and reported to be statistically significant in favor of linaclotide 72ug. This internal consistency across endpoints is reassuring and supportive of the primary endpoint results.

6.1.5.5 12 week CSBM Overall Responder within the Baseline SBM Weekly Frequency > 1 Stratum

The primary efficacy analysis was repeated in a subgroup of patients who averaged > 1 SBM/week during the 14-day Pretreatment Period. A 12-Week CSBM Overall Responder within the pre-specified stratum of baseline SBM Weekly Frequency > 1 was a patient with baseline SBM weekly frequency > 1 who meets the criteria of a 12-week CSBM Overall Responder. Among patients reporting > 1 SBM per week during the Pretreatment Period (N=226 in the placebo group, N=244 in the 72ug group, N=235 in the 145ug group), 12-week CSBM Overall Responder rates were 17.2% and 7.1% in

the linaclotide 72 ug and placebo groups, respectively. Results obtained for the linaclotide 72 ug group were consistent with results for the linaclotide 145 ug group.

Reviewer comments: Potential labeling language

(b) (4)

*was not included by the Applicant
in the draft package insert included with this sNDA.*

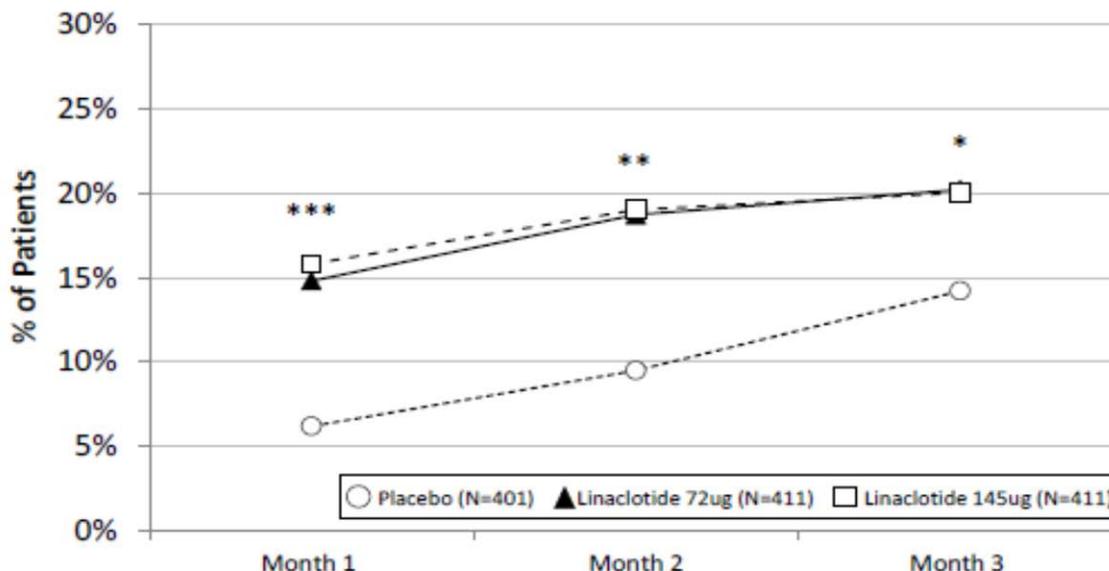
(b) (4)

6.1.5.6 Monthly CSBM Responder (Months 1, 2, and 3)

A Month 1,2, and 3 (Weeks 1 to 4 inclusive, Weeks 5 to 8 inclusive, and Weeks 9 to 12 inclusive, respectively) CSBM Responder was a patient who was a CSBM weekly responder for at least 3 of the 4 weeks in Month 1,2, and 3, respectively of the Treatment Period.

As shown in Figure 6, for Months 1, 2, and 3 of the Treatment Period, the percentage of CSBM Monthly Responders in the linaclotide 72 ug group (14.8%, 18.7%, and 20.2%, respectively) were greater than those in the placebo group (6.2%, 9.5%, and 14.2%, respectively), with the greatest treatment differences seen at Months 1 and 2. The percentages of CSBM Monthly Responders in the linaclotide 145 ug group were also greater than in the placebo group for all 3 months of the Treatment Period.

Figure 6 CSBM Responders by Month of Treatment (ITT Population)



* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$

CMH = Cochran-Mantel-Haenszel

P-values for each linaclotide dose versus placebo were obtained from the CMH tests controlling for baseline SBM stratum and geographic region.

Data Source: Section 14, Tables 14.4.2.6, 14.4.2.7, and 14.4.2.8

Source: Applicant's Figure 5, CSR, pg. 103.

Reviewer comments: *These findings provide additional data supporting the durability of response over the 12 week treatment period.*

6.1.5.7 Change from baseline in 12-week Abdominal Bloating

Abdominal bloating was measured daily using an 11-point numerical rating scale (NRS). The patient's abdominal bloating score for the Treatment Period was the average of the non-missing daily abdominal bloating scores reported by the patient during the 12-week Treatment Period. The LS mean change from baseline in Abdominal Bloating for the linaclotide 72 ug group (-1.4) was reported to show a greater improvement (decrease) from baseline compared with placebo (-1.1), ($p = 0.0063$). The LS mean change from baseline in Abdominal Bloating for the linaclotide 145 ug group (-1.5; $p < 0.0001$) was similar to the linaclotide 72 ug group.

6.1.5.8 Change from baseline in 12-week Abdominal Discomfort

Abdominal discomfort was measured daily using an 11-point NRS. The patient's abdominal discomfort score for the Treatment Period was the average of the non-missing daily abdominal discomfort scores reported by the patient during the 12-week

Treatment Period. The LS mean change from baseline in Abdominal Discomfort for the linaclotide 72 ug group (-1.3) was reported to show a numerically greater improvement (decrease) than placebo (-1.1), ($p = 0.1028$). The LS mean change from baseline in Abdominal Discomfort for the linaclotide 145 ug group (-1.4; $p = 0.0056$) was similar to the linaclotide 72 ug group.

Reviewer comments: Please note that the following comments are in reference to Sections 6.1.5.1 through 6.1.5.8: The Applicant asserts that 9 of 10 secondary endpoints were statistically significant. None have been proposed to be included in the labeling of the 72ug dose, however improvements in CSBM frequency, SBM frequency, stool consistency, and straining already exist in the label as they pertain to the pivotal trials supporting original approval, and may be informative for labeling of this lower dose in CIC.

6.1.6 Other Endpoints

Additional efficacy parameters were explored to provide additional support for the primary and secondary efficacy parameters, and were considered as exploratory.

- CSBM (SBM) within 24 Hours of Receiving the First Dose of Study Drug: 17.3% of patients in both linaclotide dose groups experienced a CSBM within 24 hours of taking their first study drug dose, compared with 13.0% of placebo patients. 45.3% of patients in the linaclotide 72 ug group and 45.5% of patients in the linaclotide 145 ug group experienced an SBM within 24 hours compared with 37.4% of patients in the placebo group.
- Change from Baseline in 12-Week Abdominal Pain: The LS mean change from baseline in Abdominal Pain for the linaclotide 72 ug group (-1.2) showed numerically greater improvement (decrease) than placebo (-1.0), and was similar to the LS mean change in the linaclotide 145 ug group (-1.3).
- Change from Baseline in 12-Week Constipation Severity: The LS mean changes from baseline in Constipation Severity for the linaclotide 72 ug (-0.9) and 145 ug (-1.0) groups showed numerically greater improvement (decreases) than placebo (-0.6).
- 12-Week Degree of Relief of Constipation Symptoms Responder: 36.0% of patients in both the linaclotide 72 ug and 145 ug groups reported being at least “somewhat relieved” for all 12 weeks of the Treatment Period, or either “considerably relieved” or “completely relieved” for at least 6 of 12 weeks of the Treatment Period, compared with 24.2% of placebo patients.
- Treatment Satisfaction: At each visit (weeks 2,4,8,12), Treatment Satisfaction was higher for both the linaclotide 72 ug and 145 ug groups versus the placebo group.
- Change from Baseline in 12-Week Percent of Days with Use of Per-Protocol Rescue Medicine: There were slight increases (< 1) in the percent of days of

rescue medicine use for patients in the linaclotide 72 ug and linaclotide 145 ug groups. A slight decrease was noted for the placebo group (-0.5).

Reviewer comments: The additional exploratory endpoints in general appears supportive of the primary endpoint. In the 72ug group, the change from baseline in 12-week percent of days with use of per-protocol rescue medicine was slightly higher than the 145ug group. However, the increases were small (< 1% of days), and would not be expected to impact the primary efficacy outcome.

The following health outcomes analyses were based on the ITT Population:

- Patient Assessment of Constipation – Quality of Life (PAC-QOL) is an instrument that measures quality of life of patients with constipation: Numerical decreases (improvements) from baseline were seen for both linaclotide dose groups compared with the placebo group for the overall PAC-QOL and all 4 subscales (Worries/Concerns, Satisfaction, Psychosocial Discomfort, Physical Discomfort).
- EuroQol-5 Dimension (EQ-5D) is an instrument for use as a measure of health status: There were improvements reported from baseline to Week 12 in the overall utility score for all treatment groups, with greater improvements seen in both the linaclotide 72 ug and 145 ug groups compared with the placebo group.
- Work Productivity and Activity Impairment Questionnaire for Constipation (WPAI:C) is a questionnaire to measure the effect of constipation on the ability to work and perform daily activities: Improvements from baseline in measured WPAI:C parameters were seen during the Treatment Period, but there were no noteworthy differences across the treatment groups.

6.1.7 Subpopulations

Analyses of efficacy parameters in demographic subpopulations in the phase 3 trial MCP-103-309 were performed for linaclotide 72 ug. The subpopulations for these analyses were age (< 65 and ≥ 65 years), sex (male and female), body mass index (BMI; < 30 kg/m² and ≥ 30 kg/m²), race (Black or African American, Caucasian, and Other), and ethnicity (Hispanic or Latino and Not Hispanic or Latino). The analyses were performed for the primary efficacy parameter, 12-week CSBM Overall Responder; for the sensitivity analysis, 12-week CSBM Sustained Responder; and for the secondary change-from-baseline efficacy parameters, CSBM Frequency Rate, SBM Frequency Rate, Stool Consistency, Straining, and Abdominal Bloating.

Age:

The treatment effect by age for the primary efficacy parameter was generally similar. In the < 65 years group (N=362 placebo/N=375 linaclotide), the response rate in the linaclotide group was reported to be 13.3% vs. 4.7% in placebo (Δ=8.6%. In the ≥ 65 years group (N=39 placebo/N=36 linaclotide), the response rate in the linaclotide group

was reported to be 13.9% vs. 5.1% in placebo ($\Delta=8.8\%$). For the sensitivity analysis, the treatment effect was generally similar; in the < 65 years group, the response rate in the linaclotide group was 12.3% vs. 4.7% in placebo ($\Delta=7.6\%$). In the ≥ 65 years group, the response rate in the linaclotide group was 13.9% vs. 5.1% in placebo ($\Delta=8.8\%$).

Reviewer comments: The percentage of subjects aged ≥ 65 years in MCP-103-309 (~10%) was probably too small to draw any meaningful conclusions.

Gender:

In females (N=316 placebo/N=312 linaclotide), the response rate in the linaclotide group was reported to be 14.4% vs. 4.4% in placebo. In males, (N=85 placebo/N=99 linaclotide), the response rate in the linaclotide group was reported to be 10.1% vs. 5.9% in placebo. The treatment effect for the primary efficacy parameter was therefore larger in females ($\Delta=14\%$) than in males ($\Delta=10\%$). A smaller difference between linaclotide and placebo was observed in males in some parameters (e.g., stool consistency), and is explained by the Applicant by a larger placebo effect in males.

Reviewer comments: Approximately a third of the randomized subjects were male, which is reflective of the population enrolled in the pivotal trials as well as in the general CIC population. It appears that in this trial, males showed a less robust response than females. In the pivotal phase 3 trials, the opposite effect was noted (a higher percentage of males were responders at both the 145ug and 290ug doses). The conflicting response rates in males, in addition to the small numbers of males enrolled, makes it difficult to draw conclusions regarding the response to linaclotide in males, and this reviewer does not recommend any changes to the labeling based on these findings.

BMI, Race, and Ethnicity:

The treatment effect for the primary efficacy parameter was greater in the ≥ 30 kg/m² subpopulation (N=167 placebo/N=149 linaclotide) with a response rate of 20.8% linaclotide vs. 6.6% in placebo ($\Delta=14.2\%$) than in the < 30 kg/m² population (N=234 placebo/N=262 linaclotide) with a response rate of 9.2% linaclotide vs. 3.4% placebo ($\Delta=5.8\%$). Treatment effect for the primary efficacy parameter was greatest for Caucasians (N=276 placebo/N=298 linaclotide) with a response rate of 13.4% linaclotide vs. 3.3% placebo ($\Delta=10.1\%$) and less so for African Americans (N=102 placebo/N=93 linaclotide) with a response rate of 12.9% linaclotide vs. 8.8% placebo ($\Delta=4.1\%$), and was generally similar in Hispanic or Latino (N=175 placebo/N=178 linaclotide) with a response rate of 12.4% linaclotide vs. 3.4% placebo ($\Delta=9\%$) and Not Hispanic or Latino (N=226 placebo/N=233 linaclotide) with a response rate of 14.2% linaclotide vs. 5.8% placebo ($\Delta=8.4\%$).

Reviewer comments: A limitation of subgroup analyses is that some subpopulations may include only a small number of patients and may lack power to have a p-value ≤ 0.05 . While these subgroup analyses were not adjusted for multiplicity, the Applicant asserts that the p-value was below 0.05 for most of the subpopulations, and therefore

the data support the conclusion that linaclotide 72 ug treatment provides benefits to the various subpopulations within each category. The presented data supports that linaclotide 72ug provides benefit to BMI, race, and ethnicity subpopulations.

Baseline Disease Severity:

In study MCP-103-309, the efficacy of linaclotide 72 ug was evaluated in subpopulations defined as less or more symptomatic by baseline SBM frequency rate (> 1 SBM/week and ≤ 1 SBM/week); this was the definition by which patients were stratified before randomization. 226 placebo patients and 244 linaclotide patients met the criteria for less symptomatic at baseline; 175 placebo patients and 167 linaclotide patients met the criteria for more symptomatic at baseline.

Reviewer comment: *The specific subpopulation of patients who averaged more than 1 spontaneous bowel movement (SBM) per week at baseline (a less-symptomatic subpopulation) was initially thought to represent a good candidate population for the lower dose of 72 ug. However, ultimately the results were not deemed definitive by the Applicant* (b) (4)

Analyses of efficacy parameters by baseline disease severity (> 1 SBM/week and ≤ 1 SBM/week at baseline) were performed for 12-week CSBM Overall Responder; 12-week CSBM Sustained Responder; and for secondary change-from-baseline efficacy parameters including CSBM Frequency Rate, SBM Frequency Rate, Stool Consistency, and Straining. Additional analyses of efficacy by baseline disease severity were performed for 12-week CSBM Overall Responder and 12-week CSBM Sustained Responder for subpopulations based on mean baseline BSFS score (≥ 3 and < 3) and mean baseline constipation severity score (< 3.5 and ≥ 3.5).

In addition, efficacy was evaluated in subpopulations based on alternate definitions of baseline disease symptom severity, as follows:

- Mean baseline (over the 2-week Pretreatment Period) stool consistency (BSFS) score ≥ 3.0 and < 3.0 . The cut point of 3 was selected because a stool consistency of 3 on this scale is considered in the lower end of the normal range (i.e., 3 to 5)^{12,13}.
- Mean baseline (over the 2-week Pretreatment Period) constipation severity score < 3.5 and ≥ 3.5 . The cut point of 3.5 was chosen because patients with scores of 1, 2, and 3 on this 5-point scale self-rated their constipation as none, mild, or moderate, respectively, while those with scores of 4 and 5 self-rated their constipation as severe and very severe, respectively.

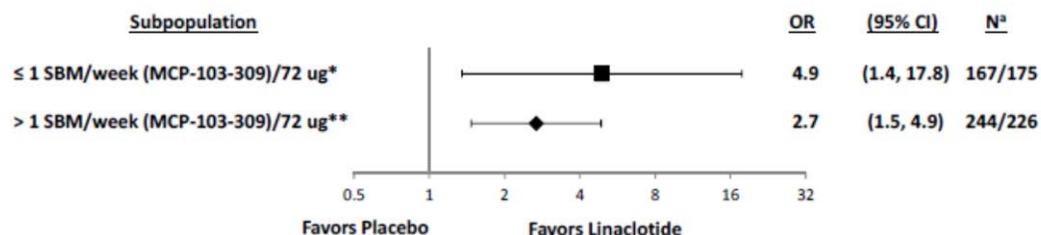
¹² Heaton KW, R. J. (1992 Jun). Defecation frequency and timing, and stool form in the general population: a prospective study. *Gut.*, 818-24.

¹³ Walter SA, K. L. (2010). Assessment of normal bowel habits in the general adult population: the Popcol study. *Scand J Gastroenterol.* p.556-66.

Reviewer Comments: The Applicant's provided literature references to support their rationale for the chosen cut points defining baseline symptoms severity by BSFS. These references were briefly reviewed by this medical officer, and the Applicant's rationale appears reasonable.

For the phase 3 primary efficacy parameter, 12-week CSBM Overall Responder, the odds ratios were reported to show improvements observed with the linaclotide 72 ug dose in the > 1 SBM/week subpopulation as well as the ≤ 1 SBM/week subpopulation. As presented in Figure 7, with linaclotide treatment, the odds of being a 12-week CSBM Overall Responder were reported to increase 2.7-fold in the > 1 SBM/week (less symptomatic) subpopulation and 4.9-fold in the ≤ 1 SBM/week (more symptomatic) subpopulation.

Figure 7 12-week CSBM Overall Responder by Baseline SBM Frequency Rate (MCP-103-309 ITT Population)



* p ≤ 0.05; ** p ≤ 0.001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; OR = odds ratio

P-value, OR, and 95% CI were obtained from CMH tests controlling for baseline SBM stratum and geographic region.

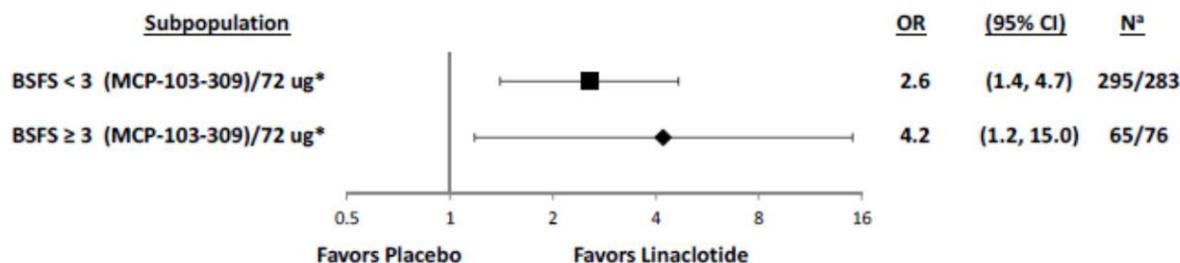
a. Linaclotide group/placebo group

Source: MCP-103-309 Table 14.4.2.5A

Source: Applicant's Table from Summary of Clinical Efficacy, page 59.

As presented in Figure 8, with linaclotide treatment, the odds of being a 12-week CSBM Overall Responder were reported to increase 4.2-fold in the BSFS score ≥ 3 (less symptomatic) subpopulation and 2.6-fold in the BSFS score < 3 (more symptomatic) subpopulation.

Figure 8 12-week CSBM Overall Responder by Baseline BSFS Score (MCP-103-309 ITT Population)



* p ≤ 0.05

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; OR = odds ratio

P-value, OR, and 95% CI were obtained from CMH tests controlling for baseline SBM stratum and geographic region.

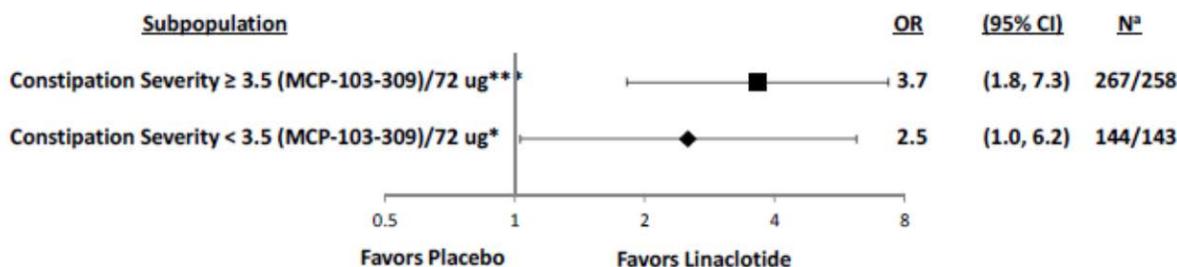
a. Linaclotide group/placebo group

Source: [After-text Table 1.1.5](#)

Source: Applicant's Table from Summary of Clinical Efficacy, page 62.

As presented in Figure 9, with linaclotide treatment, the odds of being a 12-week CSBM Overall Responder were reported to increase 2.5-fold in the < 3.5 (less symptomatic) subpopulation and 3.7-fold in the ≥ 3.5 (more symptomatic) subpopulation.

Figure 9 12-week CSBM Overall Responder by Baseline Constipation Severity Score (MCP-103-309 ITT Population)



* p ≤ 0.05; *** p ≤ 0.0001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; OR = odds ratio

P-value, OR, and 95% CI were obtained from CMH tests controlling for baseline SBM stratum and geographic region.

a. Linaclotide group/placebo group

Source: [After-text Table 1.1.6](#)

Source: Applicant's Table from Summary of Clinical Efficacy, page 64.

Reviewer comments: The odds ratios presented by the Applicant by baseline disease severity appear to show that subjects who were more symptomatic by frequency and severity (i.e., ≤ 1 SBM/week and ≥ 3.5 constipation severity score, respectively) had a higher odds ratio than the less symptomatic population. Subjects who were more symptomatic by BSFS (i.e., score <3) had a lower odds ratio than the less symptomatic

subpopulation. While these conflicting findings make it difficult to draw conclusions of response to linaclotide by baseline disease severity, it is important to note that the confidence intervals overlap for each of these subgroup analyses, and thus the results do not support a difference in efficacy by baseline disease severity. This reviewer agrees with the Applicant that the association of linaclotide response by disease severity should not be pursued in the labeling.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The approved dose for linaclotide in adult patients with CIC is 145ug. The Applicant states that patients with CIC suffer from a range of bowel symptoms of varying severities and may require individualized approaches to the management of their symptoms. They claim that CIC patients may differ in their responsiveness to treatment with linaclotide in clinical practice, and that practicing physicians have suggested that the availability of a lower dose of linaclotide may be helpful in the clinical care of some CIC patients. Therefore, the Applicant has studied the safety and efficacy of 72ug of linaclotide and are seeking approval of this dose.

The Applicant asserts that a plasma concentration-response relationship cannot be determined for linaclotide due to limited systemic absorption. Therefore, dose selection was based entirely on clinical results. The phase 2b dose-range-finding trial (MCP-103-201) that was part of the original approval application provides supportive data, and evaluated linaclotide doses of 72, 145, 290, and 579 ug. Because linaclotide 72 ug was deemed by the Applicant to demonstrate efficacy over placebo, and also had a lower incidence of diarrhea than linaclotide 145 ug in the phase 2b trial (see safety section), linaclotide 72 ug was chosen for evaluation in the phase 3 confirmatory trial (MCP-103-309). The linaclotide 145 ug dose was included in MCP-103-309 as an established positive control to evaluate assay sensitivity and to provide comparative data for the patient population treated with linaclotide 72 ug. The efficacy results, with focus on the 72ug and 145ug doses, as presented by the Applicant are discussed below.

In MCP-103-201, the reported efficacy results indicated that for almost all of the endpoints evaluated, the 72 ug dose showed a statistically significant difference from placebo. There appeared to be a dose dependency for improvement in bowel signs and symptoms (SBM and CSBM frequency, stool consistency, and straining), but not for changes in the abdominal symptoms (abdominal pain, abdominal discomfort, and bloating). The primary efficacy parameter was the change from baseline in the overall weekly SBM Frequency Rate during Weeks 1 through 4 of the Treatment Period. The secondary efficacy parameters were SBM Overall 75% Responder, CSBM Overall 75% Responder, change from baseline in the overall weekly CSBM Frequency Rate, change from baseline in overall Stool Consistency, and change from baseline in overall Straining score. Table 14 and Table 15 summarize key change-from-baseline and responder efficacy results for the 72ug and 145ug doses in the ITT Population (all

patients who received at least 1 capsule of study drug and had at least 1 post-dose evaluation of the primary efficacy assessment).

Table 14 Change-from-baseline Parameter Results (MCP-103-201 ITT Population)

Parameter	Mean Baseline	Placebo (N = 68)	Linaclotide 72 ug (N = 59)	Linaclotide 145 ug (N = 59)
		LS Mean Change from Baseline (SE)		
SBM Frequency Rate	2.2	1.4 (0.4)	2.5 (0.4)	3.1 (0.4)
CSBM Frequency Rate	0.4	0.4 (0.3)	1.4 (0.3)	1.5 (0.3)
Stool Consistency (7-point BSFS)	2.4	0.5 (0.2)	1.4 (0.2)	1.6 (0.2)
Straining (5-point scale)	3.2	-0.5 (0.1)	-0.7 (0.1)	-1.0 (0.1)
Abdominal Bloating (5-point scale)	2.8	0.0 (0.1)	-0.4 (0.1)	-0.4 (0.1)
Abdominal Discomfort (5-point scale)	2.4	0.0 (0.1)	-0.3 (0.1)	-0.3 (0.1)

Source: Applicant's Table 2-3, modified, Summary of Clinical Efficacy, pg. 22.

Table 15 Responder Parameter Results (MCP-103-201 ITT Population)

Parameter	Placebo (N = 68)	Linaclotide 72 ug (N = 59)	Linaclotide 145 ug (N = 59)
SBM 75% Responder ^a , n (%)	21 (30.9)	35 (59.3)	31 (55.4)
CSBM 75% Responder ^b , n (%)	5 (7.4)	11 (18.6)	15 (26.8)

Source: Applicant's Table 2-3, modified, Summary of Clinical Efficacy, pg. 22.

^a SBM 75% Responder: average SBM rate \geq 3/week and an increase of \geq 1 from baseline for 3 of the 4 weeks of the Treatment Period.

^b CSBM 75% Responder: average CSBM rate \geq 3/week and an increase of \geq 1 from baseline for 3 of the 4 weeks of the Treatment Period.

Reviewer comments: The results from the trial MCP-103-201 appeared generally supportive of the results from MCP-103-309. In MCP-103-201, the efficacy results appeared to demonstrate some efficacy of the 72ug dose when compared to placebo, with comparability to the 145ug dose. The change from baseline and response rates in the 72ug group were comparable to the 145ug, with the exception of the CSBM 75% responder parameter. Here the response rate in the 72ug group was less than the response rate in the 145ug group; this might be explained by the fact that the treatment

duration of this trial was 4 weeks and therefore may not have been of sufficient duration to assess response.

Demographics were generally similar among the treatment groups within each of the supporting trials (MCP-103-201 and MCP-103-309). The baseline disease characteristics underlying the secondary, change-from-baseline efficacy parameters were also generally similar among the treatment groups within each of the supporting trials. The phase 2b trial MCP-103-201 used Rome II criteria for eligibility and the phase 3 trial MCP-103-309 used Rome III criteria for eligibility. The principal difference between Rome II and Rome III criteria is the time frame of the symptom history considered for diagnosis (12 months prior to diagnosis for Rome II vs. 3 months prior to diagnosis for Rome III). The Applicant provided literature support¹⁰ of an overall diagnostic agreement rate of 96% between Rome II and Rome III criteria in the diagnosis of functional constipation within a population of Chinese patients, and therefore concluded that the difference in time frame of symptoms prior to diagnosis was not expected to result in meaningful differences between study populations. In this reviewer's opinion, the populations studied in both supportive trials were generally similar, with the exceptions outlined above and in Section 5.3.2 Protocol Summary, MCP-103-201.

In addition, the Office of Clinical Pharmacology conducted a pharmacometrics review to further explore the dose-response relationship of both linaclotide doses (72ug and 145ug). The pharmacometrics reviewer concluded that as supported by the data from the phase 3 trial, the proposed dose of 72ug appears to have similar effect compared to 145ug for the treatment of patients with CIC. Data from the phase 2b trial, when evaluated by baseline characteristics, showed a less consistent relationship, perhaps due to different treatment duration or other baseline characteristic of the treated population. Dr. Jee Eun Lee states in her review that "Nevertheless, based on the standalone Phase 3 study (Study 309), the proposed dose of 72 mcg QD appears to have similar effect compared to 145 mcg for the treatment of patients with CIC. This effect is consistent for both less and more symptomatic treatment population with both doses demonstrating treatment effect. Therefore, the results of study 309 support the approval 72 mcg QD for CIC." This reviewer agrees with the Dr. Lee's conclusions. Please see Dr. Jee Eun Lee's pharmacometrics review dated 12/2/2016 for details.

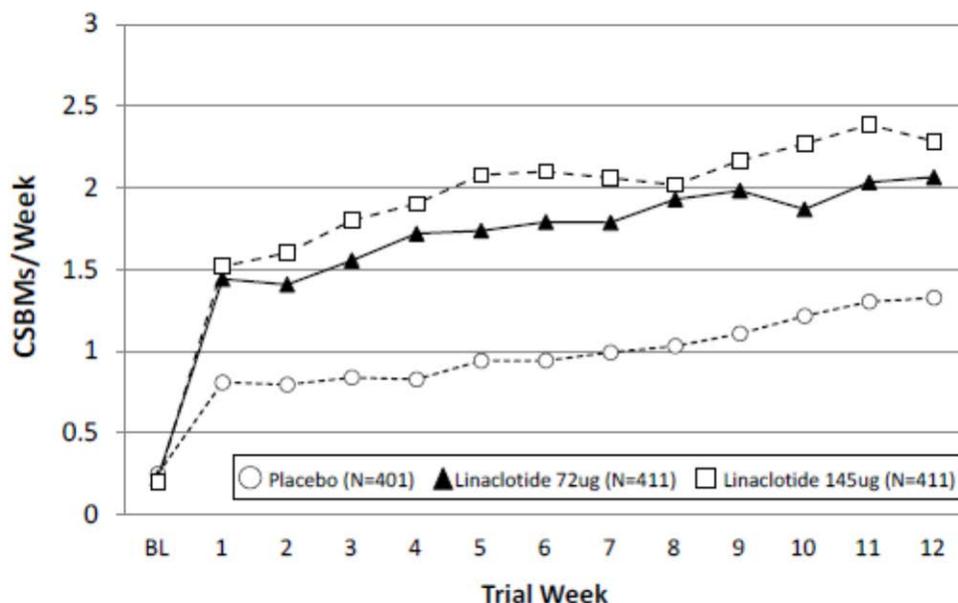
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy is discussed with evaluation of the prespecified sensitivity analysis in Section 6.1.4.1, and evaluation of monthly CSBM Response in Section 6.1.5.6.

Additional analyses were conducted assessing CSBM and SBM rate by week, and for the parameters of CSBM frequency rate, SBM frequency rate, stool consistency, straining, abdominal bloating, and abdominal discomfort, the onset of treatment effects

were reported to occur within the first week of treatment and persisted over the 12-weeks of the Treatment Period. The results for the mean CSBM rate is presented in Figure 10. Similar results were seen in mean SBM rate, mean stool consistency, mean straining, mean abdominal bloating, and mean abdominal discomfort by week.

Figure 10 Mean CSBM Rate by Week (Treatment Period; ITT Population)



Source: Applicant's Figure 7, CSR, pg. 108

Reviewer comments: These results, in addition to the Sustained and Monthly analyses of the CSBM Responder parameter in MCP-103-309 appears to support that the response to linaclotide 72ug is sustained over time.

6.1.10 Additional Efficacy Issues/Analyses

MCP-103-309 was the only adequate and well-controlled study submitted in this sNDA to support linaclotide 72ug. MCP-103-201, a phase 2 dose-ranging study, was provided as supportive evidence for the 72ug dose, and the pivotal trials conducted for the original approval of linaclotide provided evidence of efficacy and safety in CIC for a higher dose (145ug).

Per the Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, FDA may rely on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. This reviewer concludes that MCP-103-309, with the pivotal studies and the supportive phase 2 study, together represent substantial evidence of effectiveness.

In addition, MCP-103-309 had the following attributes that, based on the Guidance referenced above, make it amenable for consideration as sufficient scientific and legal basis for approval:

- Large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen. The study's internal consistency lessens concerns about lack of generalizability of the findings or an inexplicable result attributable only to the practice of a single investigator.
- Analysis of the results were generally consistent across centers, subgroups, and endpoints, demonstrating generalizability of findings.
- Statistically very persuasive finding: The low p-value associated with the primary endpoint results (<0.0001) indicates that the result is highly inconsistent with the null hypothesis of no treatment effect.

Reviewer comments: While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. However, as the Applicant is seeking approval for a new dose strength in an indication for which linaclotide is already approved, this reviewer believes it is appropriate to rely, in part, on pertinent information from other adequate and well-controlled studies of other doses strengths for this indication, to support a single adequate and well-controlled study demonstrating effectiveness. The findings from MCP-103-309 are supported by MCP-103-201, and the 2 phase 3 trials conducted for original approval demonstrated efficacy of linaclotide at a higher dose for the same indication. This reviewer believes that the rationale provided above make it possible to rely on MCP-103-309 as a single adequate and well-controlled study to provide sufficient scientific and legal basis for approval.

7 Review of Safety

Safety Summary

Based on the safety submitted from MCP-103-309 and available postmarket data, this medical reviewer finds that the safety of linaclotide 72ug is adequate for the treatment of adults with CIC, and that no formal postmarketing Risk Evaluation and Mitigation Strategy (REMS) is required for linaclotide.

A total of 143 patients (34.8%) in the linaclotide 72 ug group, 145 patients (35.3%) in the linaclotide 145 ug group, and 107 patients (26.7%) in the placebo group reported at least 1 TEAE during the Treatment Period. Linaclotide was generally well tolerated, and the overall incidence rates for AEs were comparable across treatment groups. The most commonly ($\geq 2\%$) reported adverse events reported by the Applicant were within the

Gastrointestinal Disorders system organ class (SOC) (24.1% and 25.8% of linaclotide 72 ug and 145 ug patients, respectively, versus 13.0% of placebo patients). The most common SOCs in which > 5% of patients in any treatment group reported TEAEs were GI Disorders (24.1% and 25.8% of linaclotide 72 ug and 145 ug patients, respectively; 13.0% of placebo patients) and Infections and Infestations (8.3% and 7.3% of linaclotide 72 ug and 145 ug patients, respectively; 6.0% of placebo patients). The number of patients with SAEs were lower in the linaclotide groups (0.7% and 0.5% in the 72 ug and 145 ug groups, respectively) than in the placebo group (1.0%). The incidence of AEs leading to discontinuation was also low, but higher in the linaclotide groups (2.9% and 4.6% in the 72 ug and 145 ug groups, respectively) than in the placebo group (0.5%). There were no deaths during the trial.

In this reviewer's assessment, no new safety signals emerge from the AE database. Diarrhea was the most common TEAE observed during the trial; reported by 19.2% in the linaclotide 72 ug arm, 22.1% in the linaclotide 145 ug arm, and 7.0% placebo patients. Diarrhea and abdominal distension were listed as more common among subjects receiving linaclotide than placebo, and these AEs are listed in the current drug label. There were 2 reported cases of colitis in MCP-103-309, one each in the 72ug and 145ug arm; neither case was clearly linked to the use of linaclotide, and both patients recovered with conservative treatment. Language currently exists in the Med Guide for subjects to seek medical attention if signs or symptoms of colitis develop, and this reviewer does not recommend any changes to the labeling based on these cases. The theoretical concern of guanylin deficiency syndrome was investigated and no events were identified in the 72ug dose group.

There were no deaths. Serious adverse events were uncommon and the proportion of patients with SAEs was similar across treatment arms.

Additional discussion regarding patients who reported diarrhea as a TEAE are provided in Section 7.3.5.1; discussion regarding ischemic colitis are provided in Section 7.3.2; and discussion regarding guanylin deficiency are provided in Section 7.3.5.2.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Data for the 72ug dose is provided from the phase 3 trial MCP-103-309 as well as the phase 2b trial MCP-103-201, and are summarized in Table 16.

Table 16 Overview of Clinical Trials in the CIC Indication with Linaclotide 72 ug

Clinical Trial	Trial Objective	Treatment(N)	Treatment Duration	N (M/F)	Eligibility Criteria
Phase 2b					
MCP-103-201: A Randomized, Multicenter, Double-blind, Placebo-controlled, Dose-range-finding, Parallel-group, Phase 2 Trial of Oral Linaclotide Acetate Administered to Patients with Chronic Constipation	Dose-range-finding, Safety, and Efficacy	Placebo (N = 69) Linaclotide 72 ug (N = 59) Linaclotide 145 ug (N = 56) Linaclotide 290 ug (N = 62) Linaclotide 579 ug (N = 63)	4 weeks of double-blind treatment	309 (8.1%/91.9%)	Rome II for Constipation
Phase 3					
MCP-103-309: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide (72 ug or 145 ug) Administered Orally for 12 Weeks to Patients with Chronic Idiopathic Constipation	Efficacy and Safety	Placebo (N = 401) Linaclotide 72 ug (N = 411) Linaclotide 145 ug (N = 411)	12 weeks of double-blind treatment	1223 (23.0%/77.0%)	Rome III for Constipation

Source: Reviewer's table, modified from Applicant's Table 2-1 from Summary of Clinical Safety, pg. 18.

Data for the linaclotide 145 ug dose within both the phase 3 trial (where it was included as a positive control) and the phase 2b dose-range finding trial are presented to facilitate comparison of the linaclotide 72 ug dose to the approved dose. The Safety Populations of MCP-103-201 and MCP-103-309 consist of all randomized patients who received ≥ 1 dose of study drug. All safety data were summarized based on the Safety Population, unless otherwise specified.

7.1.2 Categorization of Adverse Events

The sponsor coded adverse events (AEs) using the Medical Dictionary of Regulatory Activities (MedDRA) (version 17.0) and classified by MedDRA system organ class (SOC) and preferred term (PT) for MCP-103-309. Version 9.1 of MedDRA was used for coding AEs in the Phase 2b trial MCP-103-201.

Treatment-emergent AEs (TEAEs) were defined as an AE that occurred during the Treatment Period: the AE was not present prior to the date of the first dose of study drug or was present prior to the date of the first dose of study drug but increased in severity during the Treatment Period. TEAEs categorized as possibly, probably, or definitely related are considered “related TEAEs.”

The number and percentage of patients with common TEAEs, defined as TEAEs occurring in $\geq 2\%$ of patients in either linaclotide group, are summarized by SOC and preferred term.

Reviewer comments: This reviewer evaluated the appropriateness of the Applicant’s coding by comparing preferred terms to verbatim terms recorded by investigators. Coding was reasonably accurate and exceptions are described below.

For this reviewer’s analysis of TEAEs, an AE incidence count was generated from the provided ADAE dataset for the safety population of MCP-103-309. Although the Applicant’s system of AE categorization and coding was comprehensive and generally accurate, this reviewer noted a few incorrect translations of AEs from verbatim term to PTs and also noted a potential for splitting of several AEs due to separation of closely related PTs. As a result, in generating the AE incidence count, this medical officer modified PTs in the Applicant’s ADAE dataset in the following ways:

- Combined “abdominal pain,” “abdominal pain lower,” “abdominal pain upper,” and “gastrointestinal pain” as the same AE (PT “abdominal pain”).
- Combined “transaminases increased,” “alanine aminotransferase increase,” and “aspartate aminotransferase increased” as the same AE (PT “transaminases increased”) instead of three different AEs. The PT “liver function test abnormal” was kept separate as the verbatim terms for this PT did not clearly delineate whether the liver function test abnormal was a transaminase or not.
- Combined “gastroenteritis viral” and “gastrointestinal viral infection” as the same AE (PT “gastroenteritis viral”) instead of two different AEs.
- Combined “rash,” “rash papular,” “rash pruritic,” “dermatitis allergic,” “dermatitis contact” and “urticaria” as the same AE (PT “rash”).
- Combined “oropharyngeal pain” and “pharyngitis” as the same AE (PT pharyngitis).

Reviewer's comment: For completeness, this reviewer also generated AE tables using the Applicant's original version of the AE dataset to ensure accuracy of the AE data tables as presented by the Applicant in the Summary of Clinical Safety. This reviewer's findings were generally congruent with the AE data tables presented in the Summary of Clinical Safety. Therefore, it was determined that the adverse event tables provided by the Applicant are accurate and fairly represent the data they purport to display.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant's Summary of Clinical Safety presents data for the 72ug dose from the phase 2 trial MCP-103-201 separately than the phase 3 trial MCP-103-309. Pooled data was only provided by the Applicant for the 145ug dose across all phase 3 CIC trials. The Applicant reports that the pooled safety data (and the safety data in the phase 3 trial MCP-103-309) do not change the overall risk/benefit assessment for the linaclotide 145 ug dose as established in the original NDA. Discussions in this review focus on the 72ug and 145ug QD linaclotide doses from Studies MCP-103-309 and MCP-103-201.

Reviewer Comments: The Applicant's approach to presenting data for the 72ug dose from the phase 2 trial separately appears reasonable as only 2 trials investigating this specific dose were conducted, and can be easily compared.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All 1223 randomized patients received at least 1 dose of study drug and were included in the population analyzed for safety. The Safety Population consisted of 411 patients in the linaclotide 72 ug group, 411 patients in the linaclotide 145 ug group, and 401 patients in the placebo group. As presented in Table 17, mean duration of treatment was 80.1 days in the linaclotide 72 ug group, 78.0 days in the linaclotide 145 ug group, and 80.7 days in the placebo group. Total exposure (cumulative treatment duration in days/365.25) was 90.1 and 87.8 patient-years in the linaclotide 72 ug and 145 ug groups, respectively, and 88.6 patient-years in the placebo group.

Table 17 Treatment Duration (Safety Population MCP-103-309)

Treatment Duration (Days)	Placebo (N=401) n (%)	LIN 72 ug (N=411) n (%)	LIN 145 ug (N=411) n (%)
Distribution, n (%)			
1 day	1 (0.2)	0	4 (1.0)
> 1 day to <= 7 days	3 (0.7)	2 (0.5)	6 (1.5)
> 7 days to <= 30 days	10 (2.5)	20 (4.9)	17 (4.1)
> 30 days to <= 90	378 (94.3)	368 (89.5)	372 (90.5)
> 90 days	9 (2.2)	21 (5.1)	12 (2.9)
Mean	80.7	80.1	78.0
SD	14.6	16.7	19.9
Median	84.0	84.0	84.0
Min, Max	1, 105	5, 99	1, 104
n	401	411	411
Patient-Years	88.6	90.1	87.8

Source: Applicant's Table 14.3.1.1, CSR, pg. 631.

The maximum exposure specifically for the 72ug dose across all trials (phase 2 and phase 3) is presented in Table 18.

Table 18 Treatment Duration of the Treatment Periods (72ug Dose) for all Phase 2 and 3 Trials

Treatment Duration (Days)	Placebo (N=470) n (%)	LIN 72 ug (N=470) n (%)
Distribution, n (%)		
>= 1 day	470 (100)	470 (100)
>= 7 days	464 (98.7)	468 (99.6)
>= 14 days	458 (97.4)	460 (97.9)
>= 30 days	401 (85.3)	401 (85.3)
>= 60 days	372 (79.1)	376 (80.0)
>= 90 days	14 (3.0)	28 (6.0)
>= 120 days	0	0
Mean	72.7	73.5
SD	23.8	23.4
Median	84.0	84.0
Min, Max	1, 105	3, 99
n	470	470
Patient-Years	93.5	94.6

Source: Applicant's Table 100, Information Amendment dated 9/14/16.

At the time of original NDA review, it was determined that the applicant had exceeded ICH-E1A guidelines when examining CIC patient exposure to linaclotide across all studies in the developmental program. For detailed discussion, the reader is referred to Dr. Wynn's clinical review Section 7.2.1, dated 8/1/2012; a summary of the overall exposure at the time of approval follows. Across all 10 of the Phase 2 and 3 clinical trials of the clinical development program a total of 4370 patients received at least 1 dose of Linaclotide. Over 90% of these patients received the to-be-marketed doses of 145µg or 290µg. Of the 4370 patients in the Linaclotide clinical program (as of the October 11, 2010 data lock), 1627 were patients with CIC. There were 909 patients with CIC treated for at least 6 months and 745 patients with CIC treated for at least 1 year. In the Phase 3 open label long-term safety trials, there were 1129 patients with CIC exposed to Linaclotide. Total exposure time of the 1627 patients with chronic idiopathic constipation to Linaclotide was 1331 patient-years. In addition, the Applicant reports that cumulative post-marketing exposure as of 8/29/15 was approximately 560,613 patient-years.

Reviewer comments: The number of patients exposed and duration of exposure appear acceptable. The overall exposure in linaclotide's clinical development program at the time of approval met ICH-E1A guidance "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions", at higher doses than that studied in MCP-103-309; therefore, ICH guidelines do not necessarily need to be met specifically with the 72ug dose because of

substantial exposure from multiple clinical trials and in the postmarketing setting with higher doses for the same indication.

7.2.2 Explorations for Dose Response

Because linaclotide 72 ug was deemed by the Applicant to demonstrate efficacy over placebo, and also had a lower incidence of diarrhea than linaclotide 145 ug in this Phase 2b trial, linaclotide 72 ug was chosen for evaluation in the phase 3 confirmatory trial (MCP-103-309). The Applicant explored 4 linaclotide doses compared with placebo in MCP-103-201, a phase 2 dose-ranging study: 72ug, 145ug, 290ug, and 579ug QD of 28 days duration. The results from this study were compared with those from study MCP-103-309. High level efficacy and safety results from both studies are discussed below.

In MCP-103-201, across the 4 doses there was reported evidence of a dose response for the primary efficacy parameter (SBM Frequency Rate) as well as the other bowel symptoms. There appeared to be more responders at the 2 higher doses (290ug and 579ug) compared with the 2 lower doses (72 and 145 ug). Linaclotide 72 and 145 ug were reported to demonstrate similar efficacy with dose ordering for CSBM 75% Responder, SBM and CSBM Frequency Rates, Stool Consistency, and Straining. In MCP-103-309, for the responder endpoints, results with linaclotide 72 ug were similar to the results with linaclotide 145 ug. In the change-from-baseline parameters, there was evidence of dose ordering, with greater improvements from baseline observed with linaclotide 145 ug than with linaclotide 72 ug.

Reviewer comments: The efficacy results from the 2 trials appear to demonstrate that the 72ug dose is similarly efficacious than the 145ug dose.

From a safety perspective, in MCP-103-201, linaclotide 72 ug was reported to demonstrate lower diarrhea rates, less severe diarrhea, and fewer discontinuations due to diarrhea than the 145ug dose and higher doses.

7.2.3 Special Animal and/or In Vitro Testing

None was conducted or initiated to support this sNDA.

7.2.4 Routine Clinical Testing

The Sponsor performed monitoring of safety parameters including vital signs, physical exams, and laboratory testing. See Section 7.4.2 Laboratory Findings, Section 7.4.3 Vital Signs, and Section 7.4.4 Electrocardiograms (ECGs).

Reviewer comments: In this reviewer's assessment, the routine clinical testing of subjects in this sNDA was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Linaclotide is minimally absorbed with low systemic availability following oral administration, and 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.

As per the approved labeling, 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). 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 anticipated. There were no safety-related pharmacodynamics or pharmacokinetics trials of linaclotide submitted with this sNDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Another member of the guanylate cyclase C (GC-C) agonist class, plecanatide, is currently under review by the Division, and is undergoing evaluation of similar safety concerns as those identified with linaclotide including, but not limited to, ischemic colitis, guanylin depletion, weight gain, and diarrhea. Similar to linaclotide, plecanatide will be contraindicated in patients <6 years, and its Applicant will be required to fulfill PMR(s) assessing the potential risk of exaggerated GC-C agonist pharmacology that could cause a significant fluid shift into the intestine leading to severe dehydration in younger patients.

7.3 Major Safety Results

Table 19 presents a summary of all AEs in MCP-103-309.

Table 19 Summary of Adverse Events in MCP-103-309 (Safety Population)

	Placebo (N=401) n (%)	Linaclotide	
		72 ug (N=411) n (%)	145 ug (N=411) n (%)
TEAE	107 (26.7)	143 (34.8)	145 (35.3)
Deaths	0	0	0
Serious AEs	4 (1.0)	3 (0.7)	2 (0.5)
AEs leading to discontinuation	2 (0.5)	12 (2.9)	19 (4.6)
Severe TEAE	10 (2.5)	9 (2.2)	14 (3.4)
Related TEAE	35 (8.7)	90 (21.9)	100 (24.3)
Diarrhea TEAE	28 (7.0)	79 (19.2)	91 (22.1)
Severe diarrhea TEAE	3 (0.7)	2 (0.5)	10 (2.4)

Source: Modified Applicant's Table 2-3, Summary of Clinical Safety, pg. 20.

Reviewer comments: The AEs experienced in the linaclotide treatment groups were low, but higher in the 72 ug and 145 ug groups than in the placebo group. With the exception of the number of patients with Serious AEs (3 SAEs in linaclotide 72ug compared with 2 SAEs in linaclotide 145ug), patients in the linaclotide 72ug group suffered less adverse events when compared with the 145ug group. In particular, AEs of diarrhea appeared to occur more frequently with linaclotide 145ug. This will be discussed further in Section 7.5.1 Dose Dependency for Adverse Events. Given these findings, the 72ug dose may be slightly better tolerated than the currently approved 145 ug dose for CIC.

In the phase 2b dose-ranging trial MCP-103-201, TEAEs were reported by 31.9%, 35.6%, 32.1%, 29%, and 38.1% of patients in the placebo, 72ug, 145ug, 290ug and 579µg groups, respectively.

Reviewer comments: The TEAE incidence rates from MCP-103-201 and MCP-103-309 for both the 72ug and 145ug doses appear comparable. Although the rates of TEAEs were higher in the 72ug group than the 145ug group in the phase 2b trial (vs. higher in the 145ug group than in the 72ug group in the phase 3 trial), there were only approximately 60 patients in each treatment group, thus the absolute numbers of AEs were small and the differences between groups were small and generally within a narrow range (32-36%).

7.3.1 Deaths

No deaths were reported during this trial. No deaths were reported in MCP-103-201.

7.3.2 Nonfatal Serious Adverse Events

On-therapy Serious Adverse Events (SAEs) were SAEs that occurred on or after the date of the first dose of study drug and within 30 days of the last dose of study drug. On-therapy SAEs were experienced in 9 patients: 3(0.7%) in the 72 ug group, 2 (0.5%) in the linaclotide 145 ug group, and 4 (1.0%) in the placebo group. A list of the 9 patients who experienced an on-therapy SAE is presented in Table 20.

Table 20 List of Patients with On-therapy^a Serious Adverse Events (MCP-103-309 Safety Population)

Treatment Group	Patient ID	Age (yrs)	Sex	SAE Start Day	SAE Stop Day	Severity/Relationship	Preferred Term
Placebo	(b) (6)	43	F	76	99	Mild/Unrelated	Intraductal proliferative breast lesion
		25	F	3	7	Severe/Unlikely	Constipation ^b
		66	F	76	79	Moderate/Unrelated	Gastrointestinal hemorrhage
		60	M	27	28	Moderate/Unrelated	Asthma
Linaclotide 72 ug		70	F	50	52	Moderate/Unrelated	Hypotension ^c
		67	M	54	56	Severe/Unrelated	Azotemia
				54	56	Severe/Unrelated	Peptic ulcer
Linaclotide 145 ug		40	F	56	71	Severe/Unlikely	Colitis ^b
		34	F	25	35	Severe/Possible	Colitis ^b
		21	F	49	53	Severe/Unlikely	Diabetes mellitus inadequate control

Data source: Section 14, Table 14.5.2.4

- On-therapy SAEs were defined as SAEs that occurred on or after the date of the first dose of study drug and within 30 days of the last dose of study drug.
- The patient discontinued prematurely because of this SAE.
- Study drug was temporarily interrupted because of this SAE.

Source: Applicant's CSR, pg. 141.

One on-therapy SAE was considered by the investigator to be related to study drug (possibly, probably, or definitely related): colitis SAE in the linaclotide 145 ug group (Patient (b) (6)). There was one other SAE of colitis in the 72ug group that led to discontinuation of study drug, and was assessed by the investigator as severe and unlikely related to study drug (Patient (b) (6)). These events are briefly described below.

- Patient (b) (6), a 34-year-old white female in the linaclotide 145 ug group, had symptoms that began with worsening constipation (reported as a non-serious AE) on Day 23 that caused the patient to take four 5-mg bisacodyl tablets on Day 24. The patient developed abdominal pain and diarrhea (non-bloody; reported as a non-serious AE) and went to the emergency room on Day 26, where she was

afebrile and underwent evaluation. Abdominal exam in the ER was remarkable for guarding in the lower right quadrant but no rebound tenderness. A CBC revealed a WBC count of 15.4 K/mm³ (78% neutrophils, 13.5% lymphocytes), a hemoglobin of 12.2 gm/dL, a hematocrit of 36.9%, and a platelet count of 315 K/mm³. A computed tomography (CT) of the abdomen revealed thickening of the wall of the hepatic flexure with a length of approximately 10 cm, that was considered to be consistent with colitis, diverticulitis, or epiploic appendagitis; the CT also revealed a nonspecific increase in free fluid in the pelvis. The patient did not undergo endoscopy and was discharged home from the emergency room with hydrocodone 5 mg prn for abdominal pain and instructions to take a 10-day course of metronidazole 500 mg TID and ciprofloxacin 500 mg BID. The patient was withdrawn from the trial and recovered from the AE by Day 35. Her past medical history is remarkable for bradycardia and asymptomatic hypotension. Her concomitant meds (before the onset of the AE) included biotin, calcium with magnesium, and vitamin B-12 (all taken for health maintenance). The investigator assessed this case of colitis as severe and possibly related to study drug.

- Patient (b) (6), a 40-year-old white female in the linaclotide 72 ug group with a history of discoid lupus and depression (for which she takes bupropion and naltrexone), was hospitalized with symptoms of abdominal pain and rectal bleeding from Days 56 to 60, during which time study drug was temporarily discontinued. During the hospitalization, the patient had a BP of 95/53 mm Hg (ranged from ~130-140/80-86 at baseline) and a pulse of 68 beats per minute; a CBC revealed a WBC count of 4.4 K/mm³ (28.5% neutrophils, 53.8% lymphocytes), a hemoglobin of 10.9 gm/dL, a hematocrit of 33.9%, and a platelet count of 222 K/mm³. Her prothrombin time was 15.2 seconds (WNL=11.3 to 14.8 seconds) and her partial thromboplastin time was 38.2 seconds (WNL=22.5 to 35.0 seconds). A computed tomography (CT) of the abdomen revealed diffuse circumferential wall thickening of the descending colon that could be infectious or inflammatory; the rectum appeared normal. She did not undergo endoscopy and was treated with ciprofloxacin 500 mg BID for 10 days, metronidazole 500 mg TID for 10 days, and dicyclomine 10 mg TID for 30 days. The symptoms improved during the hospitalization, but did not completely resolve. On Day 67, the patient resumed study drug, but stopped it after taking 2 doses (last dose on Day 68) when her symptoms worsened. The patient was withdrawn from the trial and recovered from the AE by Day 71. In addition to discoid lupus and depression, the past medical history is remarkable for dyspepsia, heartburn, and vitamin D deficiency. Her only concomitant medication (before the onset of the AE, in addition to those taken for depression) was vitamin D. The investigator assessed this case of colitis as severe and unlikely related to study drug.

Reviewer comments: The role of linaclotide contributing to colitis in these cases is unclear. As discussed extensively in Dr. Wynn's clinical review of this safety concern

during review of the original application, “With the exception of the temporal relationship between the development of ischemic colitis and exposure to the possible offending agent, there is no specific clinical, laboratory, radiologic, or endoscopic finding that can distinguish drug-induced ischemic colitis from non-drug induced ischemic colitis.” The CT results for both cases are nonspecific, and neither were confirmed by biopsy to further confirm a diagnosis of ischemic colitis. Furthermore, no stool cultures, stool for ova and parasites, or *Clostridium difficile* toxin assays were obtained to rule out other causes. Patient (b) (6) appeared to have a positive rechallenge, however the patient was still symptomatic prior to restarting therapy, and additional details regarding the “worsening” of symptoms are lacking. Both patients recovered with conservative treatment.

This reviewer also examined the dataset to explore various AE terms that could signal ischemic colitis using the JReview software, to identify any additional potential cases of colitis that may have been missed due to underreporting or lack of ascertainment. Of the PTs that were searched for in the safety population (Haematochezia, Colitis, Gastrointestinal Hemorrhage, Rectal Hemorrhage, Hemoglobin decreased, Hematocrit decreased, Melena), one additional patient was identified in the 72ug (Haematochezia, Pt. # (b) (6)) and 2 additional patients in the 145ug [Rectal Hemorrhage (Pt. # (b) (6)), Hematocrit/Hemoglobin Decreased (Pt. # (b) (6))] arms. Tabular narratives for these patients were reviewed and the available clinical histories provided either did not support a diagnosis of colitis, or information was insufficient to establish causality. Specifically,

- Patient (b) (6): 46y/o M in the 72ug linaclotide group who developed hematochezia on Day 85. However, this patient also had a history of hemorrhoids which could have contributed to the hematochezia, and there was no report of abdominal pain, making the diagnosis of colitis less likely.
- Patient (b) (6): 71y/o F in the 145ug linaclotide group who developed rectal hemorrhage on Day 50. This patient had gastritis prior to treatment that could have contributed to bleeding from the rectum, and there was no report of abdominal pain, making the diagnosis of colitis less likely.
- Patient (b) (6): 45y/o M in the 145ug linaclotide group whose hemoglobin and hematocrit decreased steadily throughout the treatment period (146 to 138 to 118, 44.5 to 43.4 to 35.6). No concomitant symptoms of rectal bleeding or abdominal pain were reported, making the anemia a consequence of colitis less likely.

In this reviewer’s opinion, the available evidence supports the determination that was made during the original review of linaclotide, and do not provide additional evidence to establish a causal link between linaclotide and ischemic colitis.

This issue is further discussed in Section 8.2 Ischemic Colitis.

The other on-therapy SAEs occurring in the treatment arms were hypotension and both azotemia and peptic ulcer (in the same patient) in the linaclotide 72 ug group and diabetes mellitus, inadequate control, in the linaclotide 145 ug group. These events are briefly described below.

- Patient (b) (6), a 70-year-old white female in the linaclotide 72 ug group developed hypotension temporally associated with anesthesia provided for an outpatient L4-3 laminectomy to treat lumbosacral spondylosis on Day 50. She received a number of drugs associated with her procedure, including Cefazolin, clindamycin, Celecoxib, Propofol, rocuronium bromide, sevoflurane, IV acetaminophen, phenylephrine, Neostigmine, and ondansetron. The patient was admitted to the hospital for observation and treatment, during which time study drug was temporarily interrupted; the patient recovered and was discharged on Day 52, after which she resumed study drug and completed the trial. The investigator assessed this case of hypotension as moderate and unrelated to study drug.

Reviewer comments: This patient developed hypotension in a temporal relationship to the administration of a sedative hypnotic agent (i.e., propofol) which can cause hypotension, making the association of hypotension with linaclotide unlikely.

- Patient (b) (6), a 67-year-old white male in the linaclotide 72 ug group, had SAEs of azotemia and peptic ulcer disease (PUD). This patient had a history of chronic renal failure, hypertension, and sleep apnea, and was hospitalized with symptoms of fatigue and vomiting from Day 54 to Day 56. At the Randomization Visit, the patient's BUN was elevated [19.6 mmol/L (WNL=1.78-7.14mmol/L)] and his creatinine was also elevated [283 mcmmol/L (WNL= 62-124 mcmmol/L)]. During the hospitalization, the patient was found to have a worsening of renal function (BUN and creatinine upon hospital admission are not available) and evidence of PUD [EGD revealed hemorrhagic duodenitis, gastritis without hemorrhage, and ulceration in the duodenum and stomach (no hemorrhage in either region)], both of which had stabilized by the time he was discharged from the hospital. The patient had no previous history of peptic ulcer disease, but during the month preceding the hospitalization had received ibuprofen and prednisone to treat shoulder pain. In addition, the patient took aspirin 81 mg QD for cardioprotection; this was discontinued when the patient was discharged from the hospital. Throughout the study, the patient remained on study medicine and completed the study after being discharged from the hospital. The investigator assessed both the azotemia and the peptic ulcer as severe and unrelated to study drug.

Reviewer comments: This patient's reported SAE of azotemia is likely due to an exacerbation of chronic renal failure, as both BUN and creatinine levels were elevated prior to administration of study drug. Although this subject did not have a prior history of

PUD, there is history of ibuprofen and aspirin use, which are known to cause peptic ulcers and could have precipitated this event.

- Patient (b) (6), a 21-year-old black female in the linaclotide 145 ug group, had an SAE of diabetes mellitus inadequate control. This patient had a history of type I diabetes mellitus (for which she takes insulin glargine and insulin aspart), seizures (for which she takes levetiracetam), and migraine (for which she takes sumatriptan). On Day 49, the patient was referred to the hospital by her neurologist because of poorly controlled diabetes mellitus; the patient presented with low blood sugar and reported seizures, migraines, and vertigo. A dechallenge was initiated with levetiracetam to determine whether the primary origin of the seizures was primary epilepsy or diabetes mellitus; the results were undetermined. During hospitalization, which ended on Day 53, the patient was treated with intravenous (IV) dextrose, insulin glargine, and insulin lispro for her diabetes, as well as lorazepam for depression. The patient completed the trial. The investigator assessed this episode of diabetes mellitus inadequate control as severe and unlikely related to study drug.

Reviewer comments: This patient's reported SAE of diabetes mellitus inadequate control was likely due to the patient's underlying medical history of type 1 diabetes mellitus.

In the phase 2b trial MCP-103-201, there were no on-therapy SAEs reported in linaclotide-treated patients. This trial was reviewed with the original application for linaclotide, and further details may be found in the reviews completed for approval.

Reviewer Comments: This reviewer assessed all the non-fatal SAEs by CRFs, narratives and datasets provided by the Applicant for MCP-103-309. The overall rates of serious adverse events are low and the proportions were similar across treatment arms. Diarrhea was the most commonly reported SAE in linaclotide-treated patients, and it is included in the Warnings and Precautions of the Prescribing Information. Ischemic colitis was reported by 2 patients in the treatment arms, however available evidence is insufficient to establish a causal link between linaclotide and ischemic colitis, and in the opinion of this reviewer does not warrant further labeling. The currently approved label for linaclotide already includes a warning in the Medication Guide for patients to seek medical attention if signs or symptoms of ischemic colitis develop [i.e., unusual or severe stomach-area (abdomen) pain, especially if you also have bright red, bloody stools or black stools that look like tar].

7.3.3 Dropouts and/or Discontinuations

An adverse event leading to dropout was defined as an AE leading to permanent premature treatment discontinuation as captured on the eCRF. Table 21 provides the incidence of AEs leading to premature discontinuation by treatment group. A total of 12

patients (2.9%) in the linaclotide 72 ug group, 19 patients (4.6%) in the linaclotide 145 ug group, and 2 patients (0.5%) in the placebo group discontinued prematurely due to AEs. Diarrhea was the most common AE leading to premature discontinuation among linaclotide patients, with 10 patients (2.4%) in the linaclotide 72 ug group and 13 patients (3.2%) in the linaclotide 145 ug group. Three patients discontinued due to SAEs: two linaclotide patients (1 in the 72 ug group and 1 in the 145 ug group) discontinued due to colitis and one placebo patient discontinued due to severe constipation; the 2 events of colitis are discussed in Section 7.3.2. One additional patient in the 72ug was discontinued due to abdominal distension of moderate severity (non-serious). This was a 47y/o female patient who had abdominal distention at baseline, with multiple pre-existing conditions and concomitant medications. The abdominal distension did not significantly worsen until Week 8 of treatment with linaclotide, after which it was discontinued. The adverse event of worsening of bloating resolved 3 days later.

Reviewer comment: Regarding the patient in the 72ug group who discontinued treatment secondary to abdominal distension, it is unclear to what extent this patient's multiple co-morbidities and concomitant medications contributed to the patient's abdominal symptoms. The event (worsening of abdominal distension) occurred 1 day after initiating linaclotide, suggesting a strong temporal relationship. Linaclotide was discontinued after the event, and the response to dechallenge suggests that treatment drug played a causative role. However, this was a non-serious event that did not require hospitalization, and abdominal distension is a labeled adverse event of linaclotide.

Table 21 Incidence of Adverse Events Leading to Premature Discontinuation during the Treatment Period (MCP-103-309 Safety Population)

Adverse Event (Preferred Term)	Placebo (N=401) n (%)	Linaclotide	
		72 ug (N=411) n (%)	145 ug (N=411) n (%)
Patients with at least 1 AE leading to discontinuation	2 (0.5)	12 (2.9)	19 (4.6)
Diarrhea	0	10 (2.4)	13 (3.2)
Colitis	0	1 (0.2)	1 (0.2)
Abdominal distension	0	1 (0.2)	0
Abdominal pain	0	0	1 (0.2)
Dizziness	0	0	1 (0.2)
Hyperhidrosis	0	0	1 (0.2)
Hyperkalemia	0	0	1 (0.2)
Ligament sprain	0	0	1 (0.2)
Meniscus injury	0	0	1 (0.2)
Cholelithiasis	1 (0.2)	0	0
Constipation	1 (0.2)	0	0
Procedural pain	1 (0.2)	0	0

Data Source: Section 14, Table 14.5.2.5A
n = number of patients with AE leading to discontinuation.

Source: Applicant's CSR, pg. 142.

Within the > 1 SBM/Week Subpopulation, diarrhea led to the discontinuation of 7 (2.9%) of 244 linaclotide 72 ug patients, 10 (4.3%) of 235 linaclotide 145 ug patients, and zero placebo patients.

In MCP-103-201, no patients in the linaclotide 72 ug group discontinued due to an AE. Two patients in the linaclotide 145ug group discontinued prematurely, one of which discontinued due to diarrhea. There was a dose-related increase in the number of patients who discontinued study drug due to diarrhea [0%, 1.8%, 3.2% and 4.8% at 72ug, 145ug, 290ug and 579ug doses, respectively].

Reviewer comments: This reviewer agrees that subjects were appropriately discontinued from the study as a result of the event. Discontinuations from diarrhea appear to be dose-related, and occurred in greater frequency in the 145ug arm compared to the 72ug arm, and this is also reflected within the > 1 SBM/Week subpopulation; this pattern suggest that the 72ug dose may represent a more favorable safety profile.

7.3.4 Significant Adverse Events

The majority of the TEAEs in all treatment groups were mild or moderate in severity. A total of 9 patients (2.2%) in the linaclotide 72 ug group, 14 patients (3.4%) in the linaclotide 145 ug group, and 10 patients (2.5%) in the placebo group experienced 1 or

more TEAEs that were rated as severe. Diarrhea was the only TEAE rated as severe by more than 1 patient in a treatment group; 2 patients (0.5%) and 10 patients (2.4%) in the linaclotide 72 ug and 145 ug groups, respectively, experienced severe diarrhea, compared with 3 patients (0.7%) in the placebo group (diarrhea severity in the trial is addressed in detail in Section 7.3.5.1 Diarrhea). The only other TEAE reported as severe by more than 1 linaclotide patient in the trial was colitis (1 patient in the linaclotide 72 ug group and 1 patient in the linaclotide 145 ug group). TEAEs that were judged to be severe in at least 1 patient in either linaclotide group are presented in Table 22.

Table 22 TEAEs Reported as Severe in ≥ 1 Patient in Either Linaclotide Group during the Treatment Period (MCP-103-309 Safety Population)

Adverse Event (Preferred Term)	Placebo (N=401) n (%)	Linaclotide	
		72 ug (N=411) n (%)	145 ug (N=411) n (%)
Patients with at least 1 severe TEAE	10 (2.5)	9 (2.2)	14 (3.4)
Diarrhea	3 (0.7)	2 (0.5)	10 (2.4)
Abdominal distension	1 (0.2)	1 (0.2)	0
Colitis	0	1 (0.2)	1 (0.2)
Azotemia	0	1 (0.2)	0
Hypersensitivity	0	1 (0.2)	0
Influenza	0	1 (0.2)	0
Peptic ulcer	0	1 (0.2)	0
Toothache	0	1 (0.2)	0
Upper respiratory tract infection	0	1 (0.2)	0
Dehydration	0	0	1 (0.2)
Depression	0	0	1 (0.2)
Diabetes mellitus inadequate control	0	0	1 (0.2)
Meniscus injury	0	0	1 (0.2)
Sinusitis	0	0	1 (0.2)

Data Source: Section 14, Table 14.5.1.4

n = number of patients with severe TEAEs

Patients were counted only once within each preferred term. If severity was not available, "severe" was imputed.

Source: Applicant's CSR, pg. 134.

Reviewer comments: The incidence of severe diarrhea appears least in the 72ug group (less than placebo) as compared to the 145ug dose, supporting the lower dose strength as having a more favorable safety profile. Overall, compared with the approved dose of linaclotide 145 ug for the treatment of CIC, linaclotide 72 ug demonstrates lower diarrhea rates, less severe diarrhea, and fewer diarrhea adverse events leading to dropout.

The occurrence of other severe AEs was experienced by only 1 patient each, and do not represent a new safety signal pattern.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Diarrhea

Diarrhea was considered an AE of special interest and exploratory analyses of diarrhea TEAEs were done for trial MCP-103-309. Diarrhea was the most frequently reported TEAE by patients in any treatment group, with 79 patients (19.2%) in the linaclotide 72 ug group and 91 patients (22.1%) in the linaclotide 145 ug group reporting at least 1 episode of treatment-emergent diarrhea versus 28 patients (7.0%) in the placebo group. The majority of diarrhea TEAEs were mild in all treatment groups, however diarrhea was also the most common AE leading to discontinuation of study drug in the linaclotide groups. These findings are presented in Table 23 below.

Table 23 Summary of Diarrhea Treatment-Emergent Adverse Events during the Treatment Period (MCP-103-309 Safety Population)

	Placebo (N=401) n (%)	Linaclotide	
		72 ug (N=411) n (%)	145 ug (N=411) n (%)
Patients with at least 1 diarrhea TEAE	28 (7.0)	79 (19.2)	91 (22.1)
Severity ^a			
Mild	20 (5.0)	52 (12.7)	55 (13.4)
Moderate	5 (1.2)	25 (6.1)	26 (6.3)
Severe	3 (0.7)	2 (0.5)	10 (2.4)
Study drug action			
Treatment discontinued	0	10 (2.4)	13 (3.2)

Data Source: Section 14, Tables 14.5.1.2A, 14.5.1.4, and 14.5.2.5A

n = number of patients within a specific category

a. If a patient had more than 1 occurrence in the same event category, only the most severe occurrence was counted. If severity was not available, "severe" was imputed.

Source: Applicant's Table 28, CSR, pg. 136.

Diarrhea was assessed as related to study drug in 72 patients (17.5%) and 87 patients (21.2%) in the linaclotide 72 ug and 145 ug groups, respectively, versus 19 (4.7%) placebo patients. One patient each reported defecation urgency and fecal incontinence.

The following subsections specifically evaluate diarrhea in the context of potentially clinically significant lab or vital sign values, dehydration/dizziness/orthostatic hypotension, time of onset, and baseline diarrhea severity.

7.3.5.1.1 Patients with Diarrhea and Potentially Clinically Significant (PCS) Laboratory or Vital Sign (VS) Values

Patients who had treatment-emergent diarrhea were also assessed by the Applicant for 1) a PCS abnormal laboratory value for sodium, potassium, BUN, or creatinine; or 2) a PCS vital sign value for systolic or diastolic blood pressure, or pulse. These parameters were selected because they may be adversely affected by diarrhea and because, if they are affected, they could represent an important clinical consequence of diarrhea. Because diarrhea can be associated with volume depletion and because high BUN values (but not low BUN values) may be indicative of volume depletion, only high values for BUN were considered. No patient in any treatment group had a PCS abnormal value for sodium, potassium, BUN, or creatinine between the start and end dates of a diarrhea event. However, three patients in the linaclotide 145 ug group reported PCS high BUN values within 2 days of the start or end date of a diarrhea TEAE:

- Patient (b) (6) (a 49-year-old white female) had mild diarrhea on Day 84 and PCS high BUN the following day (9.28 mmol/L, an increase of 3.57 mmol/L from baseline; normal range 1.78-7.14 mmol/L)
- Patient (b) (6) (a 43-year-old white male) had mild diarrhea from Day 61 to Day 85 and PCS high BUN 2 days after the diarrhea resolved (8.57 mmol/L, an increase of 2.14 mmol/L from baseline)
- Patient (b) (6) (a 58-year-old black female) had moderate diarrhea from Day 4 to Day 6 (for which the patient withdrew from the study) and PCS high BUN 2 days after the diarrhea resolved (9.28 mmol/L, an increase of 2.85 mmol/L from baseline).

Reviewer comments: The high BUN values noted in temporal association with diarrhea were mildly elevated and did not appear to result in clinical dehydration.

Four additional patients in the linaclotide 145 ug group (Patients (b) (6)) had PCS high BUN values and mild or moderate diarrhea TEAEs that were not temporally associated. One patient in the linaclotide 72 ug group (Patient (b) (6) , a 44-year-old black male) had a PCS low potassium value and moderate diarrhea that was not temporally associated.

One patient in the linaclotide 145 ug group (Patient (b) (6)) had a PCS low diastolic blood pressure value measured on day 86 (98/49), in temporal association with a mild diarrhea TEAE (reported from Day 60 to Day 87); this 31 y/o white female patient had no PCS laboratory values and no other TEAEs concurrent with the low blood pressure value. Her baseline blood pressure prior to treatment was also low at 107/54. One patient in the linaclotide 145 ug group (Patient (b) (6)) had a PCS high diastolic blood pressure value and severe diarrhea that were not temporally associated. This patient had elevated blood pressures at baseline that remained elevated throughout the treatment period (160/100 – 129/91). Both patients completed the study. No other patient in any treatment group had both a diarrhea TEAE and a PCS vital sign value for blood pressure or pulse during the Treatment Period.

7.3.5.1.2 Dehydration, Dizziness, and Orthostatic Hypotension

Severe diarrhea may lead to intravascular volume depletion, and since diarrhea is the most common adverse event in patients treated with linaclotide, the Applicant specifically assessed AEs of dehydration, dizziness, and orthostatic hypotension to determine whether excessive fluid loss via the GI tract occurred in patients. Dehydration was reported by 1 patient (0.2%) in the linaclotide 145 ug group (Patient (b) (6)) and dizziness was reported by 1 patient (0.2%) each in the linaclotide 72 ug and 145 ug groups (Patients (b) (6), respectively); none of these patients reported diarrhea as an AE. Orthostatic hypotension was not reported as an AE in the Phase 3 trial MCP-103-309.

Reviewer comments: Neither reports of dehydration and dizziness were concomitantly reported with diarrhea.

7.3.5.1.3 Time of Onset of Diarrhea

The distribution of the time from first dose of study drug to first onset of treatment-emergent diarrhea is presented in Table 24. The mean time to onset of the first episode of diarrhea was 14.5 days in the linaclotide 72 ug group and 14.5 days in the linaclotide 145 ug group, compared with 39.8 days in the placebo group. In the linaclotide 72 ug group 68.4% of subjects who reported diarrhea experienced their first episode in the first 2 weeks of treatment; 64.8% of subjects in the linaclotide 145 ug group and 21.4% of placebo patients who reported diarrhea reported onset during the first 2 weeks of treatment.

Table 24 Distribution of Time to First Onset of Treatment-emergent Diarrhea during the Treatment Period (MCP-103-309 Safety Population)

	Placebo (N=401)		Linaclotide			
			72 ug (N=411)		145 ug (N=411)	
	n/N (%)	Cumulative %	n/N (%)	Cumulative %	n/N (%)	Cumulative %
Patients with at least 1 diarrhea TEAE ^a	28/401 (7.0)	--	79/411 (19.2)	--	91/411 (22.1)	--
Time of initial onset of diarrhea ^b						
Day 1	0	0	17/79 (21.5)	21.5	12/91 (13.2)	13.2
Day 2	3/28 (10.7)	10.7	10/79 (12.7)	34.2	11/91 (12.1)	25.3
Days 3-7	0	10.7	16/79 (20.3)	54.4	24/91 (26.4)	51.6
Week 2	3/28 (10.7)	21.4	11/79 (13.9)	68.4	12/91 (13.2)	64.8
Week 3	3/28 (10.7)	32.1	7/79 (8.9)	77.2	11/91 (12.1)	76.9
Week 4	4/28 (14.3)	46.4	7/79 (8.9)	86.1	9/91 (9.9)	86.8
Week ≥ 5	15/28 (53.6)	100.0	11/79 (13.9)	100.0	12/91 (13.2)	100.0

Source: Modified Applicant's Table 3-5, Summary of Clinical Safety, pg. 33

^aDenominator is the total number of patients in the treatment group.

^bDenominator is the number of patients in the treatment group who experienced a TEAE of diarrhea.

Reviewer comments: Consistent with the established linaclotide AE profile, diarrhea was the most common TEAE reported during the trial. Of the patients who developed diarrhea, over 50% appeared to do so by the second week of starting study drug. The current label for linaclotide states that the "majority of reported cases of diarrhea started within the first 2 weeks" of linaclotide treatment. This is appropriate in the opinion of this reviewer.

7.3.5.1.4 Diarrhea by Baseline Disease Severity

One rationale provided by the Applicant for developing the linaclotide 72 ug dose was to explore the hypothesis that it would result in lower diarrhea rates in patients who are less symptomatic, compared with the approved 145 ug dose. In previous linaclotide trials, patients with higher spontaneous bowel movement (SBM) frequency rates (> 1 SBM/week) had higher diarrhea rates than the overall population. Consequently, analyses of diarrhea TEAEs by baseline disease symptom severity were conducted. Because there are no established criteria for defining CIC severity, 3 parameters were

used with thresholds of baseline disease symptom severity (less symptomatic or more symptomatic) as follows:

- Mean baseline (over the 2-week Pretreatment Period) SBM frequency rate > 1 SBM/week or ≤ 1 SBM/week (prespecified).

This parameter was selected based on prior linaclotide studies where post-hoc analyses appeared to indicate that diarrhea rates were related to baseline SBM frequency; this subpopulation was prespecified for efficacy and safety analyses.

- Mean baseline (over the 2-week Pretreatment Period) stool consistency (Bristol Stool Form Scale [BSFS]) score ≥ 3.0 or < 3.0 .

A cut point of 3.0 was selected because a BSFS score of 3 is considered by the Applicant to be in the lower end of the normal range (i.e., 3 to 5) for stool consistency^{12,13}. Patients with missing baseline stool consistency were excluded from these analyses. This subpopulation was analyzed post hoc.

- Mean baseline (over the 2-week Pretreatment Period) constipation severity score < 3.5 or ≥ 3.5 .

A cut point of 3.5 was chosen because patients with scores of 1, 2, and 3 on this 5-point scale self-rated their constipation severity as none, mild, and moderate, respectively, while those with scores of 4 and 5 self-rated their constipation severity as severe and very severe, respectively. This subpopulation was analyzed post hoc.

Table 25 presents the incidence of diarrhea TEAEs by baseline disease symptom severity and treatment group. Diarrhea rates appeared to be lower in the linaclotide 72 ug group than in the linaclotide 145 ug group regardless of baseline disease severity.

Table 25 Incidence of Diarrhea Treatment-emergent Adverse Events by Baseline Disease Symptom Severity (MCP-103-309 Safety Population)

Disease Symptom Severity Definition	Placebo n/N (%)	Linaclotide	
		72 ug n/N (%)	145 ug n/N (%)
SBM frequency rate at baseline			
> 1 SBM/week	17/226 (7.5)	57/244 (23.4)	60/235 (25.5)
≤ 1 SBM/week	11/175 (6.3)	22/167 (13.2)	31/176 (17.6)
Stool consistency at baseline			
BSFS score ≥ 3.0	6/76 (7.9)	18/65 (27.7)	25/73 (34.2)
BSFS score < 3.0	19/283 (6.7)	52/295 (17.6)	59/291 (20.3)
Constipation severity at baseline			
Constipation severity score < 3.5	8/143 (5.6)	29/144 (20.1)	36/143 (25.2)
Constipation severity score ≥ 3.5	20/258 (7.8)	50/267 (18.7)	55/268 (20.5)

Source: Modified Applicant's Table 3-6, Summary of Clinical Safety, pg. 34.

Patients were counted only once within each category.

BSFS = Bristol Stool Form Scale; n = number of patients who had a diarrhea TEAE; N = number of patients in the Safety Population who met the disease symptom severity criterion; SBM = spontaneous bowel movement; TEAE = treatment-emergent adverse event.

***Reviewer comments:** The Applicant's rationale for the chosen cut points that define baseline symptoms severity appears reasonable. For stool consistency and constipation severity, the less symptomatic patients had slightly greater diarrhea rate differences between linaclotide 72 ug and 145 ug than seen in the more symptomatic patients, which may suggest that the lower dose may benefit patients who have milder CIC. However, stool consistency and constipation severity were not prespecified, the differences were small, and this trend was not seen in the prespecified SBM frequency rate. The Applicant chose not to pursue language to describe these differences in the labeling.*

7.3.5.2 Guanylin Deficiency

Due to the structural homology of endogenous guanylin peptide family members, concerns were raised that if anti-linaclotide antibodies were to develop, cross reaction with endogenous peptides could lead to deficiency syndromes. Potential clinical manifestations of loss of guanylin peptide function could include hypernatremia, volume overload, peripheral and pulmonary edema, fluid retention, weight gain, hypertension, hypernatremia, extremity swelling (excluding solitary joint swelling), and exocrine pancreatic insufficiency.

As part of this safety review, this reviewer screened the dataset to explore various AE terms that could signal guanylin deficiency using the JReview software. Of the PTs that were searched for in the safety population [peripheral edema, fluid retention, pulmonary

edema, hypertension (blood pressure increased), hypernatremia (sodium increased), weight increased, pancreatitis, lipase increased, extremity swelling, joint swelling], 4 patients were identified in the placebo arm, no patients were identified in the 72ug dose arm, and 2 patients were identified in the 145ug arm. This is summarized in Table 26.

Table 26 Adverse Events Related to Guanylin Deficiency Syndrome Reported in Linaclotide Patients in Either Treatment Group (MCP-103-309 Safety Population)

	<i>Placebo (N=401)</i>	<i>Linaclotide 72 ug (N=411)</i>	<i>Linaclotide 145 ug (N=411)</i>
Weight Increased	2 (0.5%)	0	0
Hypertension	1 (0.25%)	0	0
Hypernatremia	0	0	1 (0.24%)
Joint Effusion	0	0	1 (0.24%)
Blood Pressure Increased	1 (0.25%)	0	0
Subject Total	4 (1.0%)	0 (0%)	2 (0.49%)

Source: Reviewer's table, generated from Jreview analysis of Sponsor's AE dataset

Reviewer comments: The single patient with hypernatremia did not have any other symptoms indicative of guanylin deficiency, and had an isolated elevated sodium of 150 that returned to normal at 142. Blood pressure was within normal limits and the subject completed the study. The event of joint effusion was associated with a fall and unlikely to be a sign of volume overload/fluid retention. In this reviewer's opinion, no evidence of a signal for a clinical deficiency syndrome was identified in the clinical safety dataset submitted with this sNDA. No additional labeling language is recommended at this time, with the exception of weight gain (the reader is referred to Section 8.1.2 Weight Gain for further discussion of this issue).

Evaluation for guanylin deficiency is also being assessed in the postmarketing setting. No additional signal has been identified to date. The reader is referred to Section 8.1 Guanylin Deficiency for further discussion.

7.3.5.3 Weight Gain

The Division specifically became interested in the potential of linaclotide to cause weight changes, particularly sudden weight gain with edema, in the context of guanylin peptide deficiency after receiving information from external investigators that this may be an issue in some patients who were taking linaclotide. Specifically, the outside investigator requested that the Agency examine adverse event (AE) reports of weight gain and other serious AEs with linaclotide to determine if a change in the product labeling regarding possible "systemic effects" of linaclotide is warranted. The investigator "scanned and analyzed" online patient conversations about medications; searched (publically

available) FAERS case reports with linaclotide by 1) grave outcome incidence rate, 2) incidence of Drug ineffective and Drug effect decreased, and 3) the highest incidence AEs; and contacted 30 gastroenterologists who “regularly prescribe” linaclotide to determine if AEs were occurring in the outpatient setting. The investigator postulated that “systemic adverse effects” may be related to theoretical immunogenicity of the drug. To better evaluate the potential risk of weight gain secondary to linaclotide, DGIEP issued an IR to the Applicant to obtain additional analyses of weight data from MCP-103-309 to determine if a signal of sudden weight gain occurred at any point during the trial. The requested weight data and statistical analyses (via the 74 day letter on 6/2/16) is listed below.

- Mean weight changes from baseline to selected time points throughout the study, as well as the repeated measures analysis, to assess the change over time in each treatment arm and the comparison between arms.
- Responder analyses at specified time points to determine if a subset of patients gained a significant amount of body weight (i.e., >5% and >10%) throughout the trial.

The Applicant’s results of the body weight analyses are summarized below:

- LS mean body weight changes over the Treatment Period were similar across treatment groups (linaclotide 72 ug: -0.03kg; linaclotide 145 ug: -0.13kg; placebo: 0.24 kg).
- The median change-from-baseline values at each visit were close to zero, with a general balance of weight increases and decreases observed for each treatment group.
- The percentage of patients with body weight gains >5% and >10% did not show meaningful trends across treatment groups or visits.

Reviewer comments: The FDA statistician analyzed the Applicant’s weight data and although the numbers computed by the statistician were slightly different than that of the Applicant’s analysis, the differences did not impact the overall results. No signal for weight gain was identified in Study MCP-103-309.

7.3.5.4 Hepatic Event – Suspected Hy’s Law

There was one subject (Pt. # (b) (6)) in the linaclotide 145ug group identified by this reviewer who potentially met criteria for Hy’s Law.

An IR was sent to the Applicant on 9/15/16 requesting available data, including the patient narrative. Relevant information provided by the Applicant is summarized below:

The subject in question is a 47y/o white female randomized to receive linaclotide 145 ug once daily. As reported by the Applicant, the patient’s hepatic enzymes were elevated

prior to the first dose of study drug and continued to be elevated, but stable throughout the trial. The investigator reported no signs or symptoms related to hepatic injury during the study (physical examination revealed normal vital signs, no scleral icterus, hepatomegaly, or other findings related to hepatic disease), either at the time she entered the study or at any of the study visits after she was randomized to linaclotide. The Applicant did not consider the elevated hepatic enzymes as a TEAE, per protocol, since the elevation was present before treatment started and remained stable during treatment; therefore there was no further evaluation (e.g., liver biopsy, viral serologies, other lab or radiology tests) of the patient's elevated hepatic enzymes, either during the study or after the study was completed.

The time course of laboratory tests related to Hy's Law are provided in Table 27 below.

Table 27 Labs Related to Hy's Law

Test (ULN)	Screening (04/21/2015)		Randomization [‡] (05/19/2015)		Day 85 [†] (08/11/2015)	
	Value	x ULN	Value	x ULN	Value	x ULN
ALT (33 U/L)	84	2.5	63	1.9	80	2.4
AST (36 U/L)	123	3.4	146	4.1	182	5.1
Bilirubin (18.8 mcml/L)	73.4	3.9	54.2	2.9	66.9	3.6
Alkaline Phosphatase (115 U/L)	436	3.8	434	3.8	506	4.4
Hy's Law Met?	No		No		No	

Source: Applicant's Table 2 from IR received 9/19/16, pg. 3.

* Hy's law: All three of following must be met: (1) ALT or AST > 3 x ULN; (2) Bilirubin > 2 x ULN; (3) Alkaline Phosphatase < 2 x ULN

‡ Labs were obtained before the first dose of study drug was administered

† No labs were obtained after Day 85 (so there was no challenge and rechallenge)

ALT=alanine aminotransferase

AST=aspartate aminotransferase

ULN=upper limit of normal range

Other tests that are relevant to the etiology of the subject's elevated hepatic enzymes are provided in Table 28.

Table 28 Other Relevant Labs

Test (LLN-ULN)	Screening (04/21/2015) Value	Randomization [†] (05/19/2015) Value	Day 85 [†] (08/11/2015) Value
GGT: not obtained	-	-	-
AST / ALT ratio (LLN and ULN not specified)	1.5	2.3	2.3
Albumin (35-55 g/L) [#]	30 (L)	26 (L)	29 (L)
Creatinine (62-124 mcml/L)	35 (L)	44 (L)	27 (L)
BUN (1.78-7.14 mmol/L)	2.86	3.21	3.57
Erythrocyte mean corpuscular volume (82-102 fL)	102.0	105.6 (H)	106.1 (H)
Hemoglobin (110-155 g/L)	134	119	124
Platelet count (125-375 x 10 ⁹ /L)	98 (L)	73 (L)	100 (L)
Glucose (11.1 mmol/L)	4.27	5.00	4.94
Triglycerides: not obtained	-	-	-
Cholesterol (3.24- 5.18 mmol/L)	4.61	4.22	4.43

Source: Applicant's Table 3 from IR received 9/19/16, pg. 3.

[†] No labs were obtained after Day 85

[‡]Labs were obtained before the first dose of study drug was administered

[#] Urinalyses were not obtained during this study, so it cannot be determined if there was a renal loss of protein in this patient.

BUN=blood urea nitrogen

LLN=lower limit of normal range

ULN=upper limit of normal range

This subject was not on any concomitant medications at any time during the study, and per the Applicant had no risk factors for non-alcoholic steatohepatitis (NASH), based on referenced literature¹⁴:

- Obesity: Patients BMI (27.1 kg/m²) is not in obese range (≥ 30 kg/m²)
- Metabolic syndrome (central obesity, dyslipidemia, hypertension, and hyperglycemia): Patient has no history of any of the 4 features; her cholesterol levels, BP values, and glucose levels during the study do not suggest the presence of dyslipidemia, hypertension, or hyperglycemia.
- Type 2 diabetes mellitus (DM): Patient has no history of type 2 DM; her glucose values do not suggest the presence of insulin resistance or undiagnosed DM.
- No known history of viral hepatitis (lab tests were not obtained during the study to evaluate the elevated LFTs) or liver disease

The subject denied a history of recent alcohol abuse (i.e., during the 12 months before the Randomization Visit). Whether she had a history of alcohol abuse prior to 12 months before the Randomization Visit as well as her daily use of alcohol at trial entry and

¹⁴ Adams LA, Feldstein AE. Nonalcoholic Steatohepatitis: Risk Factors and Diagnosis. Exp Rev Gastroenterol Hepatol 2010; 4(5): 623-35.

during the trial are not known. At baseline, the urine screen for alcohol was negative. At baseline, the urine screen for benzodiazepines, cannabinoids, cocaine, opiates was negative.

The Applicant surmises that the pattern of the elevated transaminases (AST to ALT ratio greater than 2) associated with a mildly elevated alkaline phosphatase, a high erythrocyte mean corpuscular volume, and thrombocytopenia suggest that the patient may have pre-existing alcohol-induced liver injury. This possible diagnosis is also supported by the lack of risk factors for NASH, the lack of a known history of any other potential cause of hepatic disease such as viral hepatitis, and lack of concomitant medications that are associated with hepatotoxicity. In addition, in human studies, linaclotide 145 ug was minimally absorbed and would not be expected to have significant liver exposure.

Based on this information, the Applicant concludes that it is very unlikely that linaclotide was the cause of the patient's liver injury.

Reviewer comments: This subject completed the study at Week 12 and the last laboratory assessment occurred at the end of study visit (Day 85). As such, there is no dechallenge and/or rechallenge information. Her hepatic enzymes were elevated at baseline and remained relatively stable, albeit elevated throughout the entire trial. Although this patient does have elevated ALT/AST and Bilirubin meeting Hy's law criteria, she also has initial findings of cholestasis (elevated serum alkaline phosphatase) and thus does not appear to meet Hy's Law criteria (as defined by the Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation) at any time during the study. In addition, since the elevation in hepatic enzymes existed prior to study drug administration, and did not appear to uniformly increase once on treatment, this reviewer agrees with the Applicant that her liver injury is likely not caused by linaclotide. The etiology of the liver injury is unclear, and could be alcohol-induced as the Applicant suggests; the elevated alkaline phosphatase levels also are more likely to signal an obstructive basis for the elevated bilirubin, rather than hepatocellular injury. In this reviewer's opinion, the occurrence of increased hepatic enzymes in this subject does not represent a new safety signal for linaclotide, and based on this case, no further information on other possible cases of hepatitis or liver injury that occurred during the development of linaclotide is necessary at this time.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly ($\geq 2\%$) reported adverse events reported by the Applicant during MCP-103-309, presented in Table 29, were within the Gastrointestinal Disorders system organ class (SOC) (24.1% and 25.8% of linaclotide 72 ug and 145 ug patients,

respectively, versus 13.0% of placebo patients). Diarrhea was the most common TEAE, occurring in 79 patients (19.2%) in the linaclotide 72 ug group and 91 patients (22.1%) in the linaclotide 145 ug group versus 28 patients (7.0%) in the placebo group. The only other TEAE reported by the Applicant in at least 2.0% of linaclotide patients in either group was abdominal distension.

Table 29 Treatment-emergent Adverse Events Reported in \geq 2.0% of Linaclotide Patients in Either Treatment Group of MCP-103-309 and at an Incidence Greater Than Placebo (MCP-103-309 Safety Population)

<i>Adverse Event (Preferred Term)</i>	<i>Placebo (N=401) n (%)</i>	<i>Linaclotide</i>	
		<i>72 ug (N=411) n (%)</i>	<i>145 ug (N=411) n (%)</i>
Patients with at least 1 TEAE	107 (26.7)	143 (34.8)	145 (35.3)
Diarrhea	28 (7.0)	79 (19.2)	91 (22.1)
Abdominal distension	2 (0.5)	9 (2.2)	5 (1.2)

Source: Applicant's Table 3-2, Summary of Clinical Safety, pg. 25.

Patients were counted only once within each preferred term.

n = number of patients within a specific category; TEAE = treatment-emergent adverse event.

In MCP-103-201, diarrhea was also reported to be the most common TEAE, occurring in 3 patients (5.1%) in the linaclotide 72 ug group and 5 patients (8.9%) in the linaclotide 145 ug group versus 2 patients (2.9%) in the placebo group. Other TEAEs that were experienced by at least 2.0% of linaclotide patients in either the 72 ug or 145 ug group and with incidence greater than that of placebo are provided in Table 30.

Table 30 Treatment-emergent Adverse Events Reported in $\geq 2.0\%$ of Linaclotide 72 ug or 145 ug Patients in MCP-103-201 and at an Incidence Greater Than Placebo (MCP-103-201 Safety Population)

Adverse Event (Preferred Term)	Placebo (N=69) n (%)	Linaclotide	
		72 ug (N=59) n (%)	145 ug (N=56) n (%)
Patients with at least 1 TEAE	22 (31.9)	21 (35.6)	18 (32.1)
Diarrhea	2 (2.9)	3 (5.1)	5 (8.9)
Abdominal pain	3 (4.3)	2 (3.4)	5 (8.9)
Nausea	1 (1.4)	2 (3.4)	2 (3.6)
Urinary tract infection	1 (1.4)	1 (1.7)	2 (3.6)
Bronchitis	2 (2.9)	2 (3.4)	0
Influenza	0	0	2 (3.6)

Patients were counted only once within each preferred term.

n = number of patients within a specific category; TEAE = treatment-emergent adverse event.

Source: Applicant's Table 3-1, Summary of Clinical Safety, pg. 25.

***Reviewer comments:** Based on the known safety profile of linaclotide, in this reviewer's assessment, the common AEs reported by the Applicant (those reported in $\geq 2\%$ of linaclotide subjects in both the phase 2 and 3 trial and in a larger percentage of linaclotide subjects than placebo subjects) were appropriately selected. Diarrhea and abdominal pain are already reported in the current linaclotide labeling, as are upper respiratory tract infection and sinusitis. The other AEs reported in $\geq 2.0\%$ of linaclotide patients at an incidence greater than placebo (nausea, urinary tract infection, bronchitis, and influenza) occurred in a very small number of subjects (1-2) and likely do not represent a significant safety signal.*

In both trials, diarrhea was the most common TEAE, and the incidence of diarrhea was greater than placebo in both treatment arms. There also appears to be consistent dose-related increases in both trials in the incidence of diarrhea. The decreased incidence of diarrhea in the 72ug dose may contribute to a better tolerability profile than the approved 145ug dose.

7.4.2 Laboratory Findings

7.4.2.1 Hematology and Chemistry

Only parameters for which at least 1 patient had a PCS value below the lower limit of normal (LLN) or above the upper limit of normal (ULN) are presented. The incidence of PCS post-baseline hematology values was reported to be $< 1\%$ in all treatment groups. The incidence of PCS post-baseline chemistry values was $\leq 3.1\%$ in all treatment groups. A higher percentage of patients in the linaclotide 145 ug group (3.1%) had PCS

high BUN compared with the linaclotide 72 ug group (1.6%) and the placebo group (1.4%). A slightly higher percentage of patients in the linaclotide groups (1.6% in the 72 ug group and 1.0% in the 145 ug group) had PCS low bicarbonate compared with the placebo group (0.3%). One patient in the linaclotide 145 ug group (Patient (b) (6), 20-year-old white female) discontinued linaclotide after 7 days of treatment due to an abnormal laboratory AE hyperkalemia that was classified as mild.

7.4.3 Vital Signs

Vital signs (blood pressure, pulse rate, oral temperature, and respiratory rate) and body weight were obtained at all trial visits and evaluated using predefined PCS criteria. One subject in the linaclotide 145 ug group had an abnormal vital sign value that was reported as an SAE (hypotension, assessed as moderate in severity and unrelated to study drug). This subject is discussed in Section 7.3.5.1.1. There were no notable major differences between linaclotide-treated subjects and placebo-treated subjects.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained in this study. ECG data were assessed in the pivotal trials conducted to support linaclotide approval. On Sept 3, 2008, the Agency stated that the sponsor would not need to conduct a TQTc study given linaclotide's limited systemic absorption, and recommended that ECGs be collected in phase 3 clinical trials. In the pivotal trials, the Applicant conducted screening and end of treatment ECGs in all patients, and established a triplicate ECG program for a subset of patients to assess linaclotide's effects on QT/QTc. The reader is referred to Section 5.3.3 and 7.4.4. of the Dr. Erica Wynn's primary clinical review for additional details. Per Dr. Wynn's review, overall there were no clinically meaningful changes in ECG parameters across the treatment groups.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or trials were submitted with this sNDA.

7.4.6 Immunogenicity

The Applicant did not perform any immunogenicity testing during this trial, nor during clinical development prior to approval. During review of the original NDA submission, concern was raised regarding the potential immunogenicity of linaclotide, and reviewers from the Division of Therapeutic Proteins/Office of Biotechnology Products (DTP/OBP) were consulted regarding the need for further immunogenicity evaluation of linaclotide. Linaclotide is a small peptide, but it has multiple attributes that make it potentially immunogenic, including 3 disulphide bonds which render a more rigid tertiary structure than is typical for a 14 amino acid peptide. In addition, the ideal T cell epitopes for activation via HLA class 2 pathway are 12-18 amino acids in length, and for the HLA

class 1 pathway the epitopes are at least 9 amino acids in length. Therefore, linaclotide contains an appropriate number of amino acids to serve as a T cell epitope for either pathway. Due to the structural homology of endogenous guanylin peptide family members, if anti-linaclotide antibodies were to develop, there could be cross reaction with endogenous peptides that could lead to deficiency syndromes. To address this concern within the context of this sNDA, this reviewer screened the dataset for events related to guanylin deficiency syndrome. No signal for a deficiency syndrome was identified. This is discussed in detail in Section 7.3.5.2 Guanylin Deficiency.

(b) (4)



7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In MCP-103-201, the 72ug dose demonstrated similar-to-better tolerability relative to the other doses evaluated, based on 1) the incidence of diarrhea AEs (5% for the 72 ug dose, compared with 3%, 9%, 5%, and 14% for placebo and the 145 ug, 290 ug, and 579 ug linaclotide dose groups, respectively); 2) the incidence of diarrhea AEs resulting in study withdrawal (0 for the 72 ug dose, compared with 0, 2%, 3%, and 5% for placebo and the linaclotide 145 ug, 290 ug, and 579 ug dose groups, respectively); and 3) the overall incidence of AEs resulting in study withdrawal (0 for the 72 ug dose,

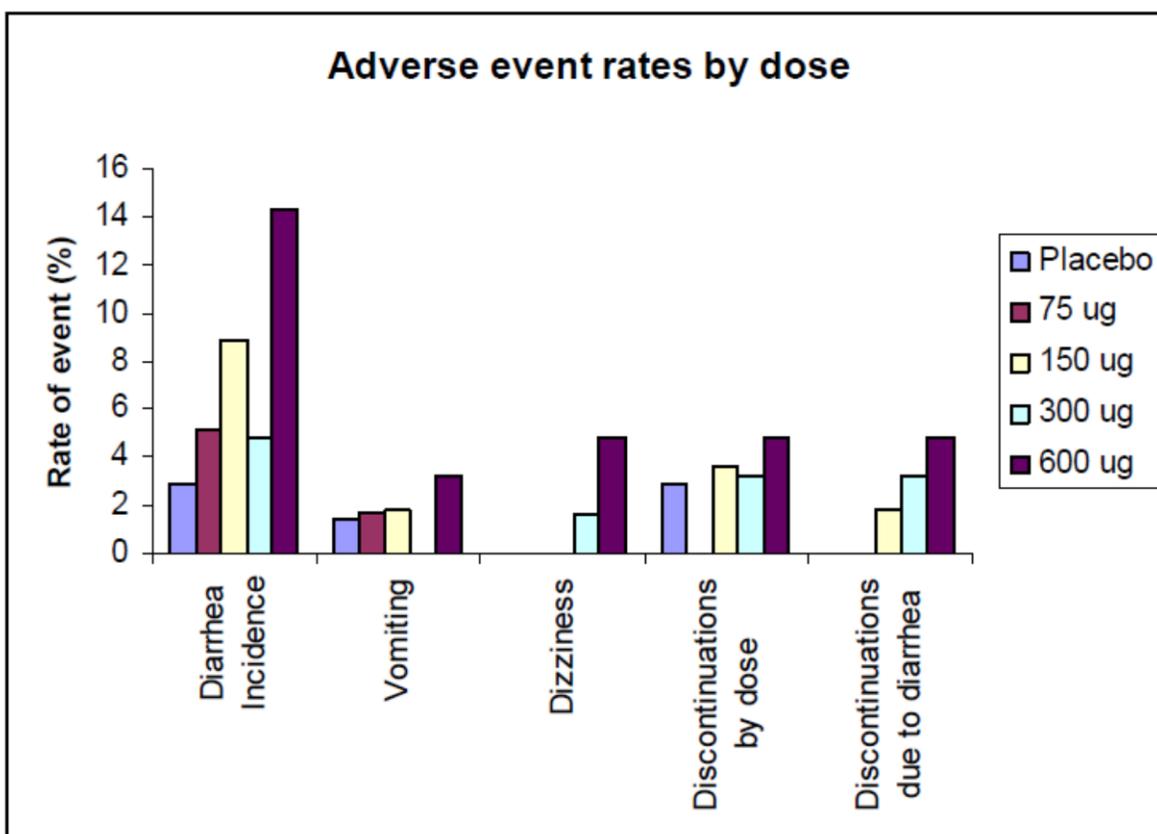
compared with 3%, 4%, 3%, and 5% for placebo and the linaclotide 145 ug, 290 ug, and 579 ug doses, respectively).

In MCP-103-309, the 72ug dose continued to demonstrate fewer instances of diarrhea, severe diarrhea, and diarrhea leading to discontinuations than the 145ug dose.

Reviewer comments: These data indicated that the 72 ug dose may be associated with a better tolerability of the most common linaclotide AE, diarrhea, compared to the approved 145ug dose.

The adverse events by dose in this phase 2 trial are presented in Figure 11. In MCP-103-309, SAEs were infrequent and balanced across treatment groups ($\leq 1\%$ of patients in any group), and the diarrhea rates, severity of diarrhea, and discontinuations due to diarrhea were lower with linaclotide 72 ug than with linaclotide 145 ug.

Figure 11 Adverse Events by Dose (MCP-103-201)



Source: Dr. Sandhya Apparaju's Clinical Pharmacology Review dated 4/6/2012, pg. 19.

Reviewer comments: Safety results from both trials demonstrate that the 72ug dose may have a better tolerability profile than the 145ug dose in terms of the most common side effect of linaclotide, diarrhea.

Please see section 6.1.8, Analysis of Clinical Information Relevant to Dosing Recommendations, as well as the Clinical Pharmacology and Pharmacometrics reviews for additional details and assessment of the exposure-response relationship.

7.5.2 Time Dependency for Adverse Events

Adverse events in the GI SOC appeared to occur more frequently early in the course of therapy. Specifically, AEs of diarrhea occurred in the majority of subjects within 2 weeks of initiating linaclotide therapy. See also Section 7.3.5.1.3 Time of Onset of Diarrhea.

Reviewer Comments: The higher rate of diarrhea AE occurring early in the course of treatment is already listed in the full prescribing information. This is acceptable to this reviewer.

7.5.3 Drug-Demographic Interactions

No formal drug-demographic studies were conducted in support of this sNDA, however, the Applicant analyzed MCP-103-309 data by age group (< 65 years; ≥ 65 years), sex (female; male), race (Caucasian; Black; Other), BMI (< 30 kg/m²; ≥ 30 kg/m²), and ethnicity (Hispanic or Latino; Not Hispanic or Latino). In the following tables that present the most common AE by demographic, the most common AEs are those that were reported in ≥ 2.0% of patients and ≥ 2 patients in either linaclotide treatment group. Patients were counted only once within each preferred term. Brief comments from this reviewer are provided following each table.

Treatment-Emergent Adverse Events (TEAEs) by Age

The majority of subjects were <65 years old (90.4%). There were minimal differences between age groups in the incidence of specific TEAEs, including diarrhea. Table 31 provides the most common AEs by age.

Table 31 Incidence of Treatment-emergent Adverse Events Reported in $\geq 2.0\%$ of Patients and ≥ 2 Patients in Either Linaclotide Treatment Group in Either Age Group (MCP-103-309 Safety Population)

Adverse Event (Preferred Term)	< 65 years			≥ 65 years		
	Placebo (N=362) n (%)	Linaclotide		Placebo (N=39) n (%)	Linaclotide	
		72 ug (N=375) n (%)	145 ug (N=368) n (%)		72 ug (N=36) n (%)	145 ug (N=43) n (%)
Patients with at least 1 TEAE	95 (26.2)	131 (34.9)	129 (35.1)	12 (30.8)	12 (33.3)	16 (37.2)
Diarrhea	25 (6.9)	72 (19.2)	83 (22.6)	3 (7.7)	7 (19.4)	8 (18.6)
Abdominal distension	2 (0.6)	9 (2.4)	3 (0.8)	0	0	2 (4.7)
Abdominal pain^a	7 (1.9)	7 (1.9)	8 (2.2)	1 (2.6)	0	0
Sinusitis	1 (0.3)	4 (1.1)	6 (1.6)	0	0	2 (4.7)
Nasopharyngitis	2 (0.6)	1 (0.3)	4 (1.1)	0	1 (2.8)	2 (4.7)

Source: Applicant's Table 6-1, modified, Summary of Clinical Safety, pg. 40.

n = number of patients within a specific category; TEAE = treatment-emergent adverse event.

^aAbdominal pain includes the preferred terms "abdominal pain", "abdominal pain upper", and "abdominal pain lower".

Reviewer comments: No single AE appears to increase with age in linaclotide subjects, however it is difficult to make conclusions regarding AE trends in the ≥ 65 year age group due to small numbers.

Treatment-Emergent Adverse Events (TEAEs) by Gender

The majority of subjects in the trial were female (77%). Diarrhea was reported less frequently by males than females in the linaclotide groups (16.2% versus 20.2% in the linaclotide 72 ug group; 17.5% versus 23.6% in the linaclotide 145 ug group; 11.8% versus 5.7% in the placebo group).

Table 32 lists the most common AEs by gender for the trial.

Table 32 Incidence of Treatment-emergent Adverse Events Reported in $\geq 2.0\%$ of Male or Female Patients in Either Linaclotide Treatment Group (MCP-103-309 Safety Population)

Adverse Event (Preferred Term)	Female			Male		
	Placebo (N=316) n (%)	Linaclotide		Placebo (N=85) n (%)	Linaclotide	
		72 ug (N=312) n (%)	145 ug (N=314) n (%)		72 ug (N=99) n (%)	145 ug (N=97) n (%)
Patients with at least 1 TEAE	88 (27.8)	117 (37.5)	118 (37.6)	19 (22.4)	26 (26.3)	27 (27.8)
Diarrhea	18 (5.7)	63 (20.2)	74 (23.6)	10 (11.8)	16 (16.2)	17 (17.5)
Abdominal distension	2 (0.6)	8 (2.6)	4 (1.3)	0	1 (1.0)	1 (1.0)
Abdominal pain^a	8 (2.5)	7 (2.2)	8 (2.5)	0	0	0
Sinusitis	1 (0.3)	4 (1.3)	6 (1.9)	0	0	2 (2.1)
Nasopharyngitis	2 (0.6)	0	5 (1.6)	0	2 (2.0)	1 (1.0)
Depression	0	0	0	0	0	2 (2.1)

Source: Applicant's Table 6-2, modified, Summary of Clinical Safety, pg. 41.

n = number of patients within a specific category; TEAE = treatment-emergent adverse event.

^aAbdominal pain includes the preferred terms "abdominal pain", "abdominal pain upper", and "abdominal pain lower".

Reviewer comments: Although diarrhea appears to be more common among both male and female subjects receiving linaclotide when compared to placebo, it is difficult to make conclusions regarding AE trends in the male group due to small numbers.

Treatment-Emergent Adverse Events (TEAEs) by Race

The majority of subjects in the trial were Caucasian (71%). There were minimal differences between race groups in the incidence of specific TEAEs, including diarrhea. Table 33 provides the most common AEs by race for the trial.

Table 33 Incidence of Treatment-emergent Adverse Events Reported in $\geq 2.0\%$ of Patients and ≥ 2 Patients of Any Race in Either Linaclotide Treatment Group (MCP-103-309 Safety Population)

Adverse Event (Preferred Term)	Caucasian			Black			Other		
	Placebo (N=276) n (%)	Linaclotide		Placebo (N=102) n (%)	Linaclotide		Placebo (N=23) n (%)	Linaclotide	
		72ug (N=298) n(%)	145 ug (N=294) n (%)		72ug (N=93) n(%)	145 ug (N=94) n (%)		72ug (N=20) n(%)	145 ug (N=23) n (%)
Patients with at least 1 TEAE	67 (24.3)	107 (35.9)	109 (37.1)	34 (33.3)	31 (33.3)	31 (33.0)	6 (26.1)	5 (25.0)	5 (21.7)
Diarrhea	15 (5.4)	60 (20.1)	69 (23.5)	12 (11.8)	17 (18.3)	20 (21.3)	1 (4.3)	2 (10.0)	2 (8.7)
Abdominal distension	2 (0.7)	5 (1.7)	7 (1.7)	0	4 (4.3)	0	0	0	0
Abdominal pain ^a	5 (1.8)	6(2.0)	6 (2.0)	3 (2.9)	1 (1.1)	1 (1.1)	0	0	1 (4.3)
Sinusitis	1 (0.4)	3(1.0)	7 (2.4)	0	1 (1.1)	1 (1.1)	0	0	0
Flatulence	3 (1.1)	3 (1.0)	3 (1.0)	2 (2.0)	1 (1.1)	0	0	2(10.0)	0
Depression	0	0	0	0	0	2 (2.1)	0	0	0

Source: Applicant's Table 6-3, modified, Summary of Clinical Safety, pg. 42.

n = number of patients within a specific category; TEAE = treatment-emergent adverse event.

^aAbdominal pain includes the preferred terms "abdominal pain", "abdominal pain upper", and "abdominal pain lower".

Reviewer comments: Diarrhea appears to be more common than placebo in all race groups receiving linaclotide; however, it is difficult to make conclusions regarding AE trends in the Black and Other group due to small numbers.

Treatment-Emergent Adverse Events (TEAEs) by BMI

Approximately a third of patients in the trial had a BMI ≥ 30 kg/m². This group had a higher percentage of Black patients compared with the lower BMI (< 30 kg/m²) group (31.1% versus 18.9%). The incidence of diarrhea was higher among patients in the higher BMI group compared with the lower BMI group in the linaclotide 72 ug (25.5% versus 15.6% in the linaclotide 72 ug group); however, the opposite was seen in the linaclotide 145 ug group (18.5% in the higher BMI group versus 24.4% in the lower BMI group). Table 34 provides the most common AEs by BMI for the trial.

Table 34 Incidence of Treatment-emergent Adverse Events Reported in $\geq 2.0\%$ of Patients in Either Linaclotide Treatment Group in Either BMI Group (MCP-103-309 Safety Population)

Adverse Event (Preferred Term)	< 30 kg/m ²			≥ 30 kg/m ²		
	Placebo (N=234) n (%)	Linaclotide		Placebo (N=167) n (%)	Linaclotide	
		72 ug (N=262) n (%)	145 ug (N=254) n (%)		72 ug (N=149) n (%)	145 ug (N=157) n (%)
Patients with at least 1 TEAE	60 (25.6)	89 (34.0)	92 (36.2)	47 (28.1)	54 (36.2)	53 (33.8)
Diarrhea	15 (6.4)	41 (15.6)	62 (24.4)	13 (7.8)	38 (25.5)	29 (18.5)
Abdominal distension	0	5 (1.9)	3 (1.2)	2 (1.2)	4 (2.7)	2 (1.3)
Abdominal pain ^a	5 (2.1)	7 (2.7)	4 (1.6)	3 (1.8)	0	4 (2.5)
Upper Respiratory Tract Infection	4 (1.7)	6 (2.3)	3 (1.2)	1 (0.6)	2 (1.3)	6 (3.8)
Sinusitis	0	2 (0.8)	2 (0.8)	1 (0.6)	2 (1.3)	6 (3.8)
Bronchitis	0	1 (0.4)	2 (0.8)	2 (1.2)	3 (2.0)	1 (0.6)

Source: Applicant's Table 6-4, modified, Summary of Clinical Safety, pg. 44.

n = number of patients within a specific category; TEAE = treatment-emergent adverse event.

^aAbdominal pain includes the preferred terms "abdominal pain", "abdominal pain upper", and "abdominal pain lower".

Reviewer comments: The incidence of diarrhea appears higher among patients in the higher BMI group compared with the lower BMI group in the linaclotide 72 ug; however, the opposite was seen in the linaclotide 145 ug group. These conflicting results make it difficult to draw inferences regarding diarrhea trends by BMI group.

Treatment-Emergent Adverse Events (TEAEs) by Ethnicity

The incidence of TEAEs reported overall was notably lower among Hispanic/Latino patients compared with Not Hispanic/Latino patients across all treatment groups, including the placebo group (16.9% versus 48.5% in the linaclotide 72 ug group; 24.6% versus 43.2% in the linaclotide 145 ug group; 13.1% versus 37.2% in the placebo group). This trend was observed for most of the common TEAEs, including diarrhea. Table 35 provides the most common AEs by ethnicity for the trial.

Table 35 Incidence of Treatment-emergent Adverse Events Reported in $\geq 2.0\%$ of Hispanic/Latino or Not Hispanic/Latino Patients in Either Linaclotide Treatment Group (MCP-103-309 Safety Population)

	Hispanic/Latino			Non-Hispanic/Latino		
	Linaclotide			Linaclotide		
Adverse Event (Preferred Term)	Placebo (N=175) n (%)	72 ug (N=178) n (%)	145 ug (N=175) n (%)	Placebo (N=226) n (%)	72 ug (N=233) n (%)	145 ug (N=236) n (%)
Patients with at least 1 TEAE	23 (13.1)	30 (16.9)	43 (24.6)	84 (37.2)	113 (48.5)	102 (43.2)
Diarrhea	4 (2.3)	13 (7.3)	25 (14.3)	24 (10.6)	66 (28.3)	66 (28.0)
Abdominal distension	1 (0.6)	2 (1.1)	2 (1.1)	1 (0.4)	7 (3.0)	3 (1.3)
Abdominal pain ^a	1 (0.6)	2 (1.1)	2 (1.1)	7 (3.1)	5 (2.1)	6 (2.5)
Flatulence	2 (1.1)	1 (0.6)	0	3 (1.3)	5 (2.1)	3 (1.3)
Sinusitis	0	0	1 (0.6)	1 (0.4)	4 (1.7)	7 (3.0)
Upper respiratory tract infection	0	0	4 (2.3)	5 (2.2)	6 (2.6)	2 (0.8)
Nasopharyngitis	0	0	0	2 (0.9)	2 (0.9)	6 (2.5)

Source: Applicant's Table 6-5, modified, Summary of Clinical Safety, pg. 45.

n = number of patients within a specific category; TEAE = treatment-emergent adverse event.

^aAbdominal pain includes the preferred terms "abdominal pain", "abdominal pain upper", and "abdominal pain lower".

Reviewer comments: While the AE rates appear higher in non-Hispanic/Latino groups compared to Hispanic/Latino groups, this is also the case in the placebo arm, so this reviewer does not believe this is related to the drug-demographic interaction. It is possible that unidentified demographic or cultural differences may explain some of these reporting differences, or this may be a chance occurrence as subgroup analyses were not controlled for multiplicity. This reviewer believes the risk-benefit still favors linaclotide in the demographic groups assessed, and does not recommend any specific information related to drug-demographic interactions be included in the labeling at this time.

7.5.4 Drug-Disease Interactions

No analyses were performed to evaluate any relationship between treatment response and past and/or concurrent illness.

7.5.5 Drug-Drug Interactions

Linaclotide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses; therefore, no systemic drug-drug interactions or drug interactions mediated by plasma protein binding of linaclotide or its metabolite are anticipated by the Applicant, and no analyses were performed to evaluate any relationship between treatment response and concomitant therapy.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies have been performed.

7.6.2 Human Reproduction and Pregnancy Data

A total of 4 on-therapy pregnancies were reported during the trial, including 1 pregnancy in the linaclotide 72 ug group, 2 pregnancies in the linaclotide 145 ug group, and 1 pregnancy in the placebo group. In all 4 patients, study drug was discontinued when the trial center was informed of the pregnancy. Pregnancy outcomes are as follows: One pregnancy (in the linaclotide 145 ug group) led to the birth of a healthy male baby (no further details are available) and 1 pregnancy (in the placebo group) was electively terminated for social reasons; pregnancy outcomes were not available for the remaining 2 pregnancies (1 each in the linaclotide 72 ug and 145 ug groups) as the patients were lost to follow-up.

As of 8/29/15, the Applicant reports that in the entire linaclotide development program, 45 pregnancies were recorded in patients who were receiving linaclotide. The pregnancy outcome is known for 35 of the 45 pregnancies. There were 20 babies born at or near term (36 weeks or more), 3 ectopic pregnancies, and 3 spontaneous abortions; 9 patients had an elective termination, including 8 for social reasons and 1 for a suspicion of trisomy 21 (unconfirmed). Among the 20 babies, one had a minor congenital malformation (polydactyly).

Reviewer comments: In animal data, the potential for linaclotide to cause teratogenic effects was studied in rats, rabbits and mice. No maternal toxicity and no effects on embryo-fetal development were seen after oral administration of up to 100,000 mcg/kg/day in rats and 40,000 mcg/kg/day in rabbits. In mice, oral dose levels of at least 40,000 mcg/kg/day produced severe maternal toxicity including death, reduction of gravid uterine and fetal weights, and effects on fetal morphology. Oral doses of 5000 mcg/kg/day did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice. The maximum recommended human dose is approximately 5 mcg/kg/day, based on a 60-kg body weight. However, animal and human doses should

not be compared directly for evaluating relative exposure as limited systemic exposure to linaclotide was achieved at the tested dose levels in animals, whereas no detectable exposure occurred in humans.

As reflected in the currently approved label, there are no adequate and well-controlled studies in pregnant women, and linaclotide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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.

A PMR clinical study to detect linaclotide and its metabolite in breast milk (PMR 1915-7) is ongoing at the time of this review. This PMR is entitled “A milk-only lactation trial in lactating women receiving Linzess (linaclotide) therapeutically to assess concentrations of linaclotide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Nursing Mothers’ subsection of the labeling”. The clinical study number is LIN-PK-01. A final report submission is due to FDA in October 2017.

7.6.3 Pediatrics and Assessment of Effects on Growth

The contents of the Pediatric Study Plan (PSP) submitted for this sNDA are in the context of existing Post Marketing Requirements (PMRs), clinical trial protocols, and Proposed Pediatric Study Plan (PPSR). A Written Request was issued by FDA on 3/11/2016. The Sponsor plans to use this plan to satisfy requirements of the Pediatric Research Equity Act (PREA) as well as the Best Pharmaceuticals for Children Act (BPCA).

Reviewer comments: The current labeling includes a boxed warning contraindicating linaclotide use in pediatric patients up to 6 years of age secondary to nonclinical study findings of deaths due to dehydration in young juvenile mice. See Section 2.4.1 Severe Dehydration for further discussion.

A study to measure GC-C mRNA levels in duodenal and colonic tissue in children ages (b) (4) years of age is currently ongoing to support PMR 2825-1, (b) (4). A list of pediatric PMRs (PREA and FDAAA Safety) and ongoing/planned clinical trials are provided in Table 36.

Table 36 Pediatric Post Marketing Commitments (PREA and FDAAA Safety)

PMR No. and Title	Protocol No./ Title/ IND Number	Status
1915-1 A nonclinical study in neonatal and juvenile mice to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide.	(b) (4)	Fulfilled (June 23, 2014)
2161-3: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 6 to 17 years treated with Linzess (linaclotide).	(b) (4)	Ongoing, FDA Final Protocol Acknowledgment letter dated 08/28/2015
2825-1: A study to measure GC-C mRNA levels in duodenal and colonic tissue obtained from children ages 0 to 6 years of age	(b) (4)	Ongoing, FDA Final Protocol Acknowledgment letter dated 7/8/2015
2161-2: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 2 to 5 years treated with Linzess (linaclotide).	(b) (4)	Deferred

Source: Modified table from Applicant's PSP dated 4/15/2016, pg. 17.

As noted in the Pediatric Written Request dated 3/11/2016, the FDA has requested that the Sponsor assess the impact of linaclotide on chloride transport in a subset of Cystic Fibrosis (CF) genotypes expressed in nonclinical models. The Applicant plans to provide positive or negative evidence to determine the effect of linaclotide on the activation of the CFTR chloride channel (e.g., via an animal Cystic Fibrosis (CF) model or cell culture/line) across varying mutant CF genotypes.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Since the approval of linaclotide, 38 cases of linaclotide overdose (> 290 ug/day) were reported through spontaneous reporting as of 8/29/15. Of these, 11 were prescribed, 12 were not prescribed but were intentional, 13 were accidental, and 2 were unspecified. Of the 38 post-marketing reports, 3 were SAEs: 2 patients were hospitalized for an exacerbation of underlying disease (IBS-C) and thought to be unrelated to linaclotide treatment, and 1 patient had an episode of worsening hypertension. In 25 cases, no AEs were reported. In the remaining 10 cases, the most frequently reported AE was diarrhea (reported in 6 cases). There have been no reported cases of drug abuse.

Reviewer comments: As the 2 approved linaclotide doses did not show evidence of withdrawal or rebound worsening, the Applicant reasoned that the potential for the lower linaclotide 72 ug dose to cause withdrawal or rebound worsening would not be more likely than with the 2 higher doses; therefore, an analysis of withdrawal and rebound was not considered necessary. In the opinion of this reviewer, the Applicant's rationale is reasonable.

7.7 Additional Submissions / Safety Issues

No additional studies were submitted with this sNDA.

8 Postmarket Experience

Linaclotide 72ug is not marketed in any country; therefore, no post-marketing data are available for the linaclotide 72 ug dose. There have been no foreign marketing developments with this dose of linaclotide, such as approval of marketing in any country or withdrawal or suspension of marketing in any country.

As of 8/29/15, linaclotide (145 ug and/or 290 ug doses) was approved in the US, Canada, and Mexico for the treatment of IBS-C in adults and CIC in adults, and in the European Union (EU) and Switzerland for the treatment of moderate-to-severe IBS-C in adults. Linaclotide was first authorized by the FDA on 8/30/12. Marketing authorization was granted by the European Medicines Agency (EMA) on 11/26/12, by Swissmedic on 6/21/13 and 3/24/15, by Health Canada on 12/2/13, and by Mexican COFEPRIS on 2/17/14.

Cumulative post-marketing exposure as of 8/29/15 was approximately 560,613 patient-years. The safety data collected from post-marketing sources since the first approval in the US, as presented and discussed in periodic aggregate reports and annual reports, did not lead to a change in the US package insert (PI).

The following trials have been completed since the initial approval of linaclotide:

- LIN-MD-04: A Phase 3b trial of linaclotide 145 ug in patients with CIC and prominent abdominal bloating.
- Foreign Trials: These trials were conducted in patients with IBS-C.
- MCP-103-307: A Phase 3 trial of linaclotide 290 ug in patients with IBS-C, conducted in China and other regions.
- 0456-CL-0021: A Phase 2b dose-range-finding trial of linaclotide in Japanese patients with IBS-C.

The Applicant reports that the safety profile of linaclotide in these trials (at doses ranging from 62.5 ug to 500 ug) was consistent with that established in the original NDA. Post-marketing surveillance through 8/29/15 were not reported to yield any signals that would suggest drug interactions. No new safety risks were identified by the Applicant in these trials.

Reviewer comments: The safety concern of guanylin deficiency, including weight gain, from the development of anti-linaclotide antibodies has been examined in the postmarket setting. The reader is referred to Section 7.3.5.2 for further discussion on the evolution of this issue; guanylin deficiency in the context of the postmarketing setting is reviewed below.

8.1 Guanylin Deficiency

The FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary dated 10/1/2014 was reviewed for reports of events that might signal guanylin deficiency. This document, resulting from an evaluation by the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), summarized the postmarket safety experience 18 months after approval or after use of the product by at least 10,000 patients. New serious adverse events, known adverse events reported in an unusual number, or other new potential safety concerns were described. This safety summary covered the period of 8/30/2012 to 2/28/2014.

The postmarketing safety review identified a potential safety issue of additional complications (such as dizziness, loss of consciousness, hypotension) related to the labeled AE of diarrhea. There was one case of acute pancreatitis that was identified in a patient taking linaclotide 145ug daily. The reviewers commented that this case was confounded by the patient's previous history of alcohol abuse. This patient also experienced two additional episodes of acute pancreatitis following linaclotide discontinuation. Other events that could represent signs of guanylin deficiency, including weight gain, were not identified at the time of the review.

(b) (4)

Reviewer comments: This medical officer reviewed the postmarketing SAE report summary submitted by the Applicant and is in agreement with the Applicant's conclusion that no specific safety pattern for a clinical deficiency syndrome is identified from the data provided. Although several cases of clinically significant weight gain were identified in post-marketing by the Division of Pharmacovigilance I (DPV-I) (see Section 8.1.2 below), there is insufficient evidence to conclude that this adverse event is part of a clinical deficiency syndrome. As the role of linaclotide in causing weight gain specifically cannot be ruled out, this reviewer recommends that only language regarding weight gain should be considered for inclusion into the label (see Section 8.1.2 for discussion).

8.1.2 Weight Gain

The Division specifically became interested in the potential of linaclotide to cause weight changes, particularly sudden weight gain with edema, in the context of guanylin peptide deficiency after receiving information from external investigators that this may be an issue in some patients who were taking linaclotide. To better evaluate the potential risk of weight gain secondary to linaclotide, DGIEP issued an IR to the sponsor of linaclotide to obtain additional analyses of weight data from the clinical trials program to determine if a signal of sudden weight gain occurred at any point during the trials. The requested weight data and statistical analyses from the phase 3 program in CIC and IBS-C (via an IR on 4/25/16) were received from the Applicant on 5/6/16, and are listed below:

- Mean weight changes from baseline to selected time points throughout the study, as well as the repeated measures analysis to assess the change over time in each treatment arm and the comparison between arms.
- Responder analyses at specified time points to determine if a subset of patients gained a significant amount of body weight (i.e., >2%, >5% and >10%) throughout the trial.

DGIEP consulted the Division of Pharmacovigilance I (DPV-I) to examine the Applicant's submission, in addition to AE reports of weight gain, including online patient conversations submitted by external investigators, and other serious AEs with linaclotide to determine if a change in the product labeling regarding possible "systemic effects" of linaclotide was warranted. DPV provided the following high level summary of the Sponsor's results (the reader is referred to the DPV-1 Memorandum dated 6/2/16 for detailed discussion):

- Three sets of analyses were performed regarding changes in body weight during four phase 3 clinical trials of linaclotide in chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C).
- Least squares mean body weight changes over the Treatment Period were similar across all four trials and treatment groups (linaclotide -0.12 to 0.19 kg; placebo 0.05 to 0.26 kg).
- For each trial, the median change-from-baseline values at each visit were close to zero, with a general balance of weight increases and decreases observed for each treatment group.
- The percentage of patients with body weight gains >2%, >5%, and >10% did not show meaningful trends across treatment groups or visits.
- Review of four postmarketing clinical trials with linaclotide revealed no evidence of body weight changes.

DPV-1 also conducted a search of the FDA Adverse Event Reporting System (FAERS) and the medical literature, identifying 9 cases of clinically significant weight gain [as defined by a reported weight increase of at least 5% from baseline or an absolute weight increase of at least 3.5 kg within 6 months of starting linaclotide, and exclusion of cases if weight gain was attributable to a strong alternative cause (such as severe constipation/fecal retention) or there was lack on information to assess causality]], of which 5 were associated with a serious outcome. These cases were individually reviewed and ultimately, the DPV-1 reviewer concluded that the FAERS cases do not confirm a drug-event relationship between linaclotide and edema. However, as noted in the DPV-1 memorandum, “Without knowing the specific mechanism behind possible linaclotide-induced weight gain.....we cannot exclude the possibility that linaclotide had a role in the development of weight gain. Clinicians should be aware of this adverse event with linaclotide use, and therefore addition of this information to Section 6.2 Postmarketing Experience is reasonable.”

Reviewer comments: The Sponsor concluded that three analyses of the weight data from four phase 3 clinical trials

(b) (4)

There does not appear to be a strong safety signal from available weight gain data among patients taking linaclotide; however, this reviewer agrees with the DPV-1 recommendation that the role of linaclotide in causing this adverse event cannot be ruled out, and should be considered for inclusion in Section 6.2 of the labeling.

8.2 Ischemic Colitis

Two patients in MCP-103-309 had an SAE reported as colitis. Given this observation and because of discussions between the Agency and Sponsor about ischemic colitis during the review of the original NDA, the Sponsor searched the linaclotide database for cases of colitis (ischemic or other, but excluding confirmed cases of *C. difficile* colitis).

The reader is referred to Section 7.7 of Dr. Erica Wynn’s clinical review for detailed discussion of this safety concern at the time of original approval.

The search conducted by the Sponsor included all trials that have been conducted with linaclotide since the original NDA was submitted and yielded 2 additional cases of colitis. Information regarding the 4 cases reported in clinical trials since approval and the 3 cases from the original NDA is provided in Table 37.

Table 37 Cases of Colitis (Excluding C. difficile Colitis) in Linaclotide Clinical Trials

Trial	Patient ID	Age; Sex	IBS-C or CIC	Study Drug	AE Term	Start Date	Outcome	Investigator Causality ^a
3 Cases from Original NDA								
MCP-103-305	(b) (6)	64; F	IBS-C	290 ug/day	IC	Day 548	Recovered	Related
LIN-MD-02	(b) (6)	72; F	IBS-C	145 ug/day	IC	Day 386	Recovered	Related
MCP-103-201	(b) (6)	74; M	CIC	290 ug/day	IC	11 days after last dose ^d	Recovered	Unrelated
4 Cases Since Original NDA								
MCP-103-307 ^b	(b) (6)	63; F	IBS-C	Placebo	Colitis	10 days after last dose	Recovered	Related
0456-CL-0031 ^c	(b) (6)	38; F	IBS-C	500 ug/day	Colitis	Day 172	Recovered	Related
MCP-103-309	(b) (6)	34; F	CIC	145 ug/day	Colitis	Day 14	Recovered	Related
MCP-103-309	(b) (6)	40; F	CIC	72 ug/day	Colitis	Day 68	Recovered	Unrelated

IC = ischemic colitis

- a. Causality based on 2 categories: related or unrelated
- b. Patient enrolled in China
- c. Patient enrolled in Japan
- d. Patient had 11 days of study treatment.

Source: Reproduced from Applicant’s Summary of Clinical Safety, pg. 57.

Two patients (Patients (b) (6)) in MCP-103-309 had an SAE reported as colitis (these patients are discussed in Section 7.3.2). Two additional cases of colitis were identified post-approval (1 receiving placebo and 1 receiving 500ug), and are described below.

- Patient (b) (6) from MCP1-03-307 [China: A Phase 3, International, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Trial of Linaclotide Administered Orally for 12 Weeks to Patients with Irritable Bowel Syndrome with Constipation (IBS-C)] is a 63-year-old Asian female in the placebo group with a prior history of intestinal obstruction who presented with abdominal pain and vomiting 10 days after completion of placebo dosing. She was afebrile. A hemogram suggested acute infection, a diagnosis of colitis was made by computed tomography (CT), and the patient was hospitalized. Treatment was initiated with enrofloxacin hydrochloride for infection, pantoprazole for acid suppression, rehydration therapy and an enema. Following a bowel movement, the symptoms of abdominal pain and vomiting related to the colitis resolved and the patient was discharged after 1 day. The patient totally recovered from the AE approximately 8 days after its start. The investigator rated the event as moderate in intensity and unrelated to study drug.

- Patient (b) (6) from Study 0456-CL-0031 (Japan - Double Blinded long-term Study in IBS-C Patients) is a 38-year-old Asian female in the linaclotide 500ug group with a history of infectious enteritis who presented to her local hospital with abdominal pain, a cold sweat, diarrhea, and loss of consciousness on Day 172 of treatment (linaclotide 0.5mg). It was reported that the patient passed a bloody stool. The physical examination was reported to suggest that the source of the abdominal pain was from the abdominal wall or psychogenic in nature, and not the viscera. A colonoscopy revealed “localized ischemic redness” at the sigmoid-descending colon junction that was considered to be “transient ischemic disease” but unlikely to be the cause of the abdominal pain; no biopsy was performed. During colonoscopy, narrow band imaging showed an absence of inflammatory changes that are suggestive of ischemic colitis. A CT scan demonstrated mild splenomegaly. A serum amylase was 54 U/L (normal range: 40-120 U/L). The past history is remarkable for a history of infectious enteritis within the previous 8 months. The clinical course after diagnosis was uncomplicated; the patient was discharged within 2 days and the symptoms resolved within approximately 2 weeks with conservative treatment (famotidine PRN).

Thus, a total of 7 cases of colitis were reported in linaclotide clinical trials. It should be noted that the 3 cases from the original NDA were of ischemic colitis and the 4 cases since that submission were of colitis without any additional specification.

The Applicant provides the following rationale from the cumulative review of colitis in the linaclotide program to support the assertion that there is insufficient evidence to determine that these colitis cases are related to linaclotide treatment:

- All 3 cases of ischemic colitis from the original NDA were confirmed with biopsies and considered by a blinded panel of 5 independent gastroenterologists with expertise in ischemic colitis to be probably not related to study drug.
- Based on information provided from the investigators, the workups to evaluate the cause of colitis in the 4 cases that have been reported since the original NDA submission were as follows: 2 cases (Patients (b) (6)) had abdominal CT scans only; 1 case (Patient (b) (6)) had an abdominal CT scan and colonoscopy; 1 case (Patient (b) (6)) had no CT scan or endoscopy; no case had a colon biopsy, stool culture, stool examination for ova and parasites, or Clostridium difficile toxin assay.
- Given that the differential diagnosis of colitis is extensive and that the CT scan findings (i.e., colon thickening) are nonspecific for an etiology of colitis, there does not appear to be sufficient information to determine the etiology of the colitis in the 3 cases where either no abdominal CT scan was performed (Patient (b) (6)) or only an abdominal CT scan was performed (Patients (b) (6)). Thus, there is insufficient evidence to make a diagnosis of ischemic colitis with these cases.

- With 1 of the 4 cases (Patient (b) (6)), the investigator noted that a colonoscopy revealed localized ischemic redness at the sigmoid-descending colon junction consistent with a diagnosis of transient ischemic disease; narrow band imaging showed a retained pattern consistent with a likely circulatory disturbance but an absence of inflammatory changes suggestive of ischemic colitis. No colon biopsy was performed.
- The clinical course after diagnosis in all 7 subjects was uncomplicated; the symptoms resolved within approximately 2 weeks with conservative treatment (IV fluids and antibiotics).

Reviewer comments: The FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary dated 10/1/2014 was also reviewed for reports of ischemic colitis. Two cases were identified (both taking 145ug daily); one case was found by the reviewers to have insufficient detail for causal analysis between ischemic colitis and linaclotide. The other case occurred in a patient who experienced dehydration and acute renal failure, and was surmised by the reviewer that these events may have been a factor in the development of ischemic colitis. The reader is referred to this Postmarket Safety Summary for further detail.

The reported postmarket cases of ischemic colitis, in conjunction with the 2 cases reported in MCP-103-309 and the 2 additional colitis cases identified in postmarketing by the Applicant, prompted DGIEP to consult the Office of Safety and Epidemiology for a review of the FDA Adverse Event Reporting System (FAERS) database for cases of ischemic colitis. The OSE reviewer's conclusions are summarized here; for details the reader is referred to Lisa Harinstein's consult review dated 10/13/2016.

A FAERS search from 2/28/2014 to 9/12/2016 yielded an additional 3 cases of ischemic colitis:

- *40-year-old female experienced bloody diarrhea and ischemic colitis requiring hospitalization 1 day after starting linaclotide 145ug, and linaclotide was discontinued because of the adverse events. The outcome of the event was unknown. The reviewer surmised that the events (bloody diarrhea, ischemic colitis) occurred 1 day after initiating linaclotide, suggesting a strong temporal relationship. However, the patient had multiple comorbidities and concomitant medications were not provided; this information would be useful when assessing causality.*
- *60-year-old female experienced a diverticular bleed, severe abdominal pain, nausea, and worsening constipation requiring hospitalization 13 days after starting linaclotide 145ug, and linaclotide was discontinued. The reviewer commented that the patient was diagnosed with diverticulitis and severe constipation at the time of the diverticular bleed; both are associated with the development of ischemic colitis and provide an alternative cause for the event of ischemic colitis.*

- *43-year-old female experienced mild ischemic colitis while taking linaclotide 290ug occurring approximately 11 months after starting linaclotide, and that the patient had previously taken linaclotide 145 mcg with a dose increase to 290 mcg daily after an unknown period of time. Linaclotide was permanently discontinued after the event and the mild ischemic colitis resolved sometime the next month. The reviewer noted that information on the time between the linaclotide dose increase (145 mcg to 290 mcg) and event occurrence was not given, and would have aided in establishing whether there was a strong or weak temporal relationship between the event and linaclotide.*

The DPV-1 reviewer concluded, and this reviewer agrees, that although it may be mechanistically possible for ischemic colitis to occur in association with linaclotide, there is insufficient evidence to confirm an association between linaclotide use and ischemic colitis. A causal or contributory role of linaclotide also cannot be excluded based on the three identified FAERS cases.

Overall, the colitis cases were diverse in presentation, and were reported in both the placebo group and with various linaclotide doses. The onset of the event was at various time points during treatment or after treatment. There appear to be potential alternative explanations for the colitis cases, including the underlying conditions being treated, other preexisting conditions, and concomitant medications. In this reviewer's opinion, the available evidence supports the determination that was made during the original review of linaclotide, and do not provide additional evidence to establish a causal link between linaclotide and ischemic colitis. Therefore, this reviewer agrees that there appears to be insufficient evidence to determine that these colitis cases are related to linaclotide treatment. The current Medication Guide for linaclotide includes symptoms and management information of ischemic colitis; this reviewer believes that this is sufficient and does not recommend any addition of language to the label as it pertains to ischemic colitis.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Discussions regarding labeling recommendations are ongoing at the time of this review. For final labeling agreements, see the approved product label for Linzess®.

Regarding the proposed dosage strength of 72ug, key changes included the addition of linaclotide 72ug dosage, tolerability, and efficacy information to the labeling sections 2 Dosage and Administration, 6 Adverse Reactions, and 14 Clinical Trials.

9.3 Advisory Committee Meeting

No advisory committee (AC) meeting was held.

9.4 Prohibited Medicine (MCP-103-309)

All medicine listed in the sections below (“1-day Washout” and “14-day Washout”) are excluded during the Pretreatment and Treatment Periods. A 1-day washout means that the particular medicine is not allowed during the calendar day before the Pretreatment Visit; a 14-day washout means that the particular medicine is not allowed during the 14 calendar days before the Pretreatment Visit.

1-DAY WASHOUT (*no medicine during the calendar day before the Pretreatment Visit*)

1. Any over-the-counter or prescription laxative, suppository, or enema (e.g., polyethylene glycol, lactulose, Fleet’s) and any herbal or natural agent that a person might take for constipation. Note: The use of fiber, bulk laxatives, stool softeners (surfactants such as docusate), and probiotics is acceptable, provided the patient has been on a stable dose during the 30 days before the Screening Visit and plans to continue stable dosing throughout the trial.
2. Any medicine used to treat diarrhea (e.g., bismuth subsalicylate, kaolin)
3. NSAIDs if taken for abdominal pain or discomfort

14-DAY WASHOUT (*no medicine during the 14 calendar days before the Pretreatment Visit*)

1. Drugs with known pharmacological activity at 5-HT₄, 5-HT_{2b} or 5-HT₃ receptors (e.g., cisapride, tegaserod, ondansetron, tropisetron, granisetron, dolasetron, and mirtazapine).
2. Any treatment specifically taken for IBS-C or CIC alone or in combination, including lubiprostone, an approved chloride channel activator that enhances intestinal fluid secretion, linaclotide, plecanatide, colchicine, and misoprostol. Note: patient has taken commercially available linaclotide or participated in a linaclotide or plecanatide clinical study during the 30 days before the Screening Visit.
3. Prokinetic agents (e.g., metoclopramide, itopride, prucalopride, and domperidone).
4. Anti-cholinergic agents (e.g., dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solefenacin, darifenacin, and tropium). Note: inhaled ipratropium and tiotropium are permitted.
5. Bile acid sequestrants (e.g., cholestyramine and colestipol).
6. Cholinomimetic agents (e.g., bethanechol, pyridostigmine, tacrine, and physostigmine). Note: intraocular cholinomimetic agents (e.g., pilocarpine) are permitted.
7. Antipsychotic agents (e.g., risperidone, haloperidol, droperidol, chlorpromazine, perphenazine, all phenothiazines, quetiapine, olanzapine, and clozapine) unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit. Note: paliperidone is permitted without restriction.

8. Antidepressants unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit.

Specifically included are the following:

- Tricyclic antidepressants (e.g., amitriptyline, imipramine, and nortriptyline);
- Monoamine oxidase inhibitors (e.g., furazolidone, isocarboxazid, pargyline, phenelzine, and selegiline tranylcypromine);
- Selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, paroxetine, and citalopram);
- Serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine and desvenlafaxine succinate)
- Others (e.g., trazodone, and bupropion).

9. Calcium channel blocker verapamil unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit. Note: all other calcium channel blockers (e.g., nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine, etc.) are permitted and may be used without restriction.

10. Oral and parenteral antibiotics (However, a standard regimen [up to 10 days] of oral antibiotics is permitted.).

11. Any investigational or imported drugs that have not been approved for human use by the US FDA.

12. All narcotics either alone or in combination (e.g., tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate, and paregoric). Note: narcotics used as anesthesia for a colonoscopy require a 5 calendar day wash-out prior to the patient entering into the Pretreatment Period.

13. Any medicine taken for the purpose of losing weight (e.g., orlistat, phentermine, phendimetrazine, diethylpropion, benzphetamine, and sibutramine).

14. Any medicine that is known to cause diarrhea (e.g., acarbose).

15. Proton pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole) unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit.

16. Others: barbiturates (e.g., butalbital and phenobarbital) and chronic oral or parenteral glucocorticoids (which must be discontinued at least three months before screening; however, one 10-day course of oral or 1 injection of parenteral glucocorticoids is permitted). Pregabalin, is acceptable, provided the patient has been on a stable dose during the 30 days before the Screening Visit and plans to continue stable dosing throughout the trial.

9.5 Financial Disclosure Template

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 202811/S-010

Clinical Review
Preeti Venkataraman, MD
sNDA 202811 s-010
Linzess (Linaclotide)

Submission Date(s): 3/25/2016

Applicant: Forest Laboratories, LLC

Product: Linzess (linaclotide)

Reviewer: Preeti Venkataraman, MD

Date of Review: May 23, 2016

Covered Clinical Study (Name and/or Number): MCP-103-309

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>116</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

One investigator disclosed a financial interest as follows:

- *(b) (6) - Study MCP-103-309 (site (b) (6), principal (b) (6) investigator): For the year ending 2013, (b) (6) was a member of the speaker's bureau for the drug Linzess and earned greater than \$25,000 given his national and international expertise in this area. As a former PI of the original clinical trials and a pre-clinical investigator for linaclotide, he played an important role in measuring the effects of linaclotide on visceral sensation.*

The applicant reports that bias has been minimized in this study due to a number of critical elements that were built into the design of the Phase 3 clinical study. These design elements are described below:

- *Multicenter, double-blinded, randomized, placebo-controlled design.*
- *Patient enrollment and treatment assignment were accomplished using a centralized process.*
- *Data contributing to efficacy endpoints (patient diary information) were collected using a centralized CRO-monitored interactive voice response system (IVRS). Data were entered directly by the patients.*
- *The statistical analyses for the study were prospectively defined by the Sponsor. In order to minimize bias, the analysis for each efficacy endpoint was based on an Intent-to-Treat study population.*

The disclosed financial interests/arrangement does not appear to affect the approvability of the application or raise questions about data integrity; this investigator's site screened one patient who failed to be randomized, and therefore did not influence the efficacy results as it provided minimal contribution to study data.

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/s/

PREETI VENKATARAMAN
01/13/2017

LAURIE B MULDOWNNEY
01/13/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

PRODUCT QUALITY REVIEW(S)

**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls**

1. **NDA Supplement Number:** NDA 202-811/S-010 efficacy supplement

2. **Submission(s) Being Reviewed:**

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Supplement	Efficacy supplement	3/25/16	3/25/16	3/25/16	1/25/17	12/6/16

3. **Proposed Changes:** To introduce a new strength (72 mcg) of Linaclotide.

4. **Review #:** 2 (amendment to the original review)

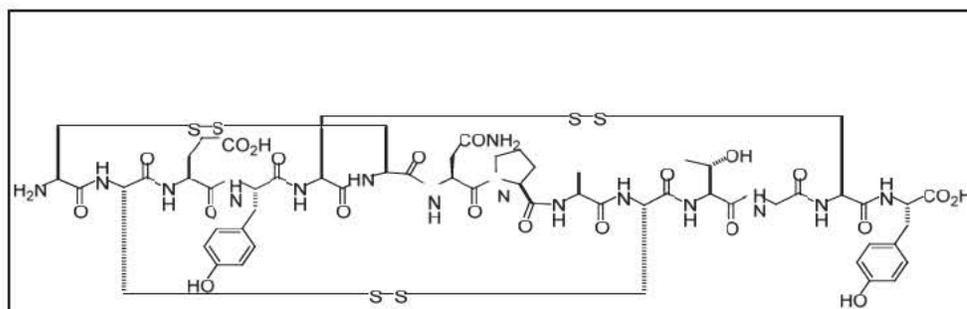
5. **Clinical Review Division:** DGIEP

6. **Name and Address of Applicant:**

Forest Laboratories, LLC
Harborside Financial Center
Plaza V, suite 1900
Jersey City, NJ, 07311

7. **Name of the Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Linaclotide	capsules	72 mcg	Oral	Rx	N/A

8. Chemical Name and Structure of Drug Substance:

Structural Formula (Absolute Stereochemistry):

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)

USAN name: linaclotide

Mwt: 1526.8 Dalton
 $C_{59}H_{79}N_{15}O_{21}S_6$

9. Indication: Irritable bowel syndrome with constipation and chronic idiopathic constipation in adults

10. Supporting/Relating Documents:

11. Consults:

Consults	Recommendation	Date	Reviewer
OPF/Facility	Approval	7/11/16	OPF
OLDP Lifecycle API	N/A		
Microbiology	N/A		
Pharm/Tox	N/A		
Biopharm	Approval	12/6/16	Dr. Kelly M. Kitchens, Ph.D.
Statistics	N/A		
DMEPA	N/A		
CDRH/ODE	N/A		
CDRH/OC	N/A		
EA	N/A		

12. Executive Summary:

This is an addendum to the previous review in order to correct a statement made in the evaluation of the Module 3.2.P.5 information "characterization of impurities" and "drug product specification".

Please refer to the review text for additional information in regard to characterization of impurities.

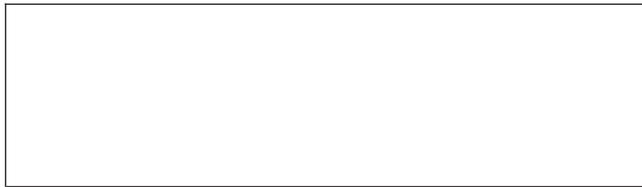
13. Conclusions & Recommendations:

From CMC's standpoint, this supplement **is recommended** for approval.

14. Comments/Deficiencies to be conveyed to Applicant: None

15. Primary Reviewer:

Hossein Khorshidi, CMC reviewer, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)



16. Secondary Reviewer:

David Lewis, Branch Chief, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ



CMC Assessment

This Supplemental New Drug Application is intended to support approval of a new (lower) 72 mcg strength of linaclotide for adult patients with chronic idiopathic constipation (CIC). This is an approved drug. Currently, the drug product is supplied as hard gelatin capsules as a 145 mcg strength for patients with CIC and as a 290 mcg strength for patients with constipation predominant irritable bowel syndrome (IBS-C).

(b) (4)



David
Lewis

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Comments: concur; this addendum clarifies a point about the control of impurities in the new 72-mcg product. Recommendation remains "approval" from the standpoint of CMC.



Hossein
Khorshidi

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Date: 1/19/2017 01:07:06PM

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**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls**

1. **NDA Supplement Number:** NDA 202-811/S-010 efficacy supplement

2. **Submission(s) Being Reviewed:**

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Supplement	Efficacy supplement	3/25/16	3/25/16	3/25/16	1/25/17	12/6/16

3. **Proposed Changes:** To introduce a new strength (72 mcg) of Linaclotide.

4. **Review #:** 1

5. **Clinical Review Division:** DGIEP

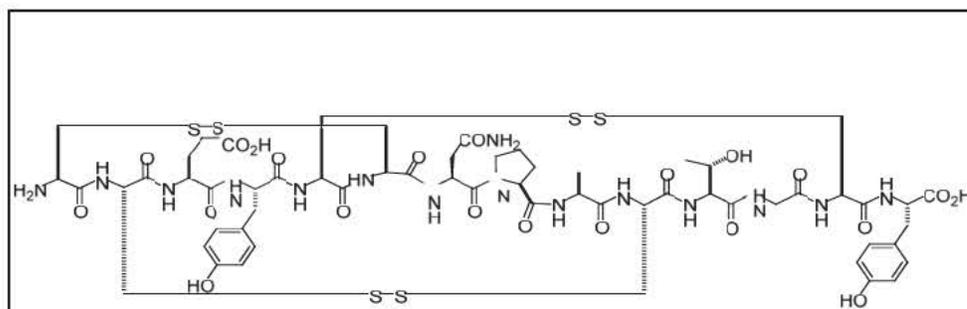
6. **Name and Address of Applicant:**

Forest Laboratories, LLC
Harborside Financial Center
Plaza V, suite 1900
Jersey City, NJ, 07311

7. **Name of the Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Linaclotide	capsules	72 mcg	Oral	Rx	N/A

8. Chemical Name and Structure of Drug Substance:



Structural Formula (Absolute Stereochemistry):

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)

USAN name: linaclotide

Mwt: 1526.8 Dalton
 $C_{59}H_{79}N_{15}O_{21}S_6$

9. **Indication:** Irritable bowel syndrome with constipation and chronic idiopathic constipation in adults

10. **Supporting/Relating Documents:**

11. **Consults:**

Consults	Recommendation	Date	Reviewer
OPF/Facility	Approval	7/11/16	OPF
OLDP Lifecycle API	N/A		
Microbiology	N/A		
Pharm/Tox	N/A		
Biopharm	Approval	12/6/16	Dr. Kelly M. Kitchens, Ph.D.
Statistics	N/A		
DMEPA	N/A		
CDRH/ODE	N/A		
CDRH/OC	N/A		
EA	N/A		

12. **Executive Summary:**

NDA 202-811/S-010 requests marketing approval for a 72 µg dose of Linzess® (linaclotide) capsules for adult patients with chronic idiopathic constipation. The currently approved strengths of Linzess® are 145 and 290 µg capsules. This submission contains efficacy (clinical, biopharmaceutical) data as well as CMC (quality) information to support the addition of the 72 µg capsules. It is noted that the qualitative composition for the 72 µg capsules is different than that for the approved 145 and 290 µg capsules. The Phase 2b dose-range-finding trial (for treatment fo CIC, by Ironwood) included clinical information of a 72-µg capsule.

For the drug substance, the applicant has referenced to manufacturers DMFs. It is noted that the drug substance suppliers are not changed from those currently approved in this NDA.

Since the manufacturing process in all above proposed drug substance manufacturing sites are similar, and produces a drug substance of similar quality (demonstrated by the above test results), therefore, it can be concluded that the produced batches (from all three commercial manufacturing sites are comparable). Under these circumstances, we may omit reviewing the corresponding DMFs (of the manufactures) for the drug substance.

(b) (4)

According to the biopharmaceutics review (Dr. Kelly M. Kitchens, Ph.D., dated 12/6/16), the provided dissolution data are acceptable from biopharmaceutical standpoint and the supplement is recommended for approval.

Based on stability data of the primary and supportive batches in addition to historical stability data of the approved linaclotide capsules (LINZESS), a shelf life of 24 months is proposed for linaclotide capsules, 72 ug in the commercial packaging of 4-count and 30-count bottle configurations when stored at controlled room temperature.

13. Conclusions & Recommendations:

From CMC's standpoint, this supplement is **recommended** for approval.

14. Comments/Deficiencies to be conveyed to Applicant: None

15. Primary Reviewer:

Hossein Khorshidi, CMC reviewer, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)



16. Secondary Reviewer:

David Lewis, Branch Chief, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ



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David
Lewis

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Comments: concur, recommend approval from the standpoint of CMC-quality.



Hossein
Khorshidi

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

NON-CLINICAL REVIEW(S)

REV-NONCLINICAL-05 (Review Noted (NAI))

NDA-202811

SUPPL-10

Supporting Document 516

New/Supplement

User Fee/Coversheet

Form 3674

Submit Date: 03/25/2016 - FDA Received Date: 03/25/2016

No nonclinical studies were submitted in this supplement. The revisions to the labeling subsections with nonclinical data (5.1, 8.1, 8.4, 12.1, 13.1, and 13.2) were developed in collaboration with the review team, which included Dr. Joette Meyer (Associate Director for Labeling), Dr. Jane Liedtka and Dr. Tamara Johnson (Maternal Health Team for subsection 8.1), Dr. Ethan Hausman and Dr. Hari Sachs (Pediatric Team for subsection 8.4), and Dr. Laurie Muldowney (Medical Team Leader).

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/s/

DAVID B JOSEPH
12/02/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Translational Sciences
 Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	202811_S10 (SDN 0161)
Drug Name:	LINZESS® (linaclotide), Oral 72 ug Dose
Indication(s):	Chronic Idiopathic Constipation (CIC), Adults
Applicant:	Forest Laboratories, Inc. and Ironwood Pharmaceuticals, Inc.
Date(s): Stamp: Filing: PDUFA:	March 25, 2016 May 24, 2016 January 25, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Team: Reviewer: Team Leader:	Shahla Farr, MS Yeh-Fong Chen, PhD
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Clinical Team: Reviewer: Team Leader: Project Manager:	Preeti Venkataraman, MD Laurie Muldowney, MD Cheronda Cherry-France, RN BSN MHA
EDR Location:	\\CDSESUB1\evsprod\NDA202811\202811.enx
Keywords:	NDA review, clinical study

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1. EXECUTIVE SUMMARY

The Sponsor conducted one phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, 12-week trial (Study MCP-103-3093) to demonstrate the efficacy of Linzess' 72 ug in treating adult patients with Chronic Idiopathic Constipation (CIC).

One concern we had for this study pertains to the female to male randomization ratio, which is larger than 3:1. When the gender subgroup was performed for the primary endpoint, the female subpopulation was highly statistically significant ($p < 0.0001$) whereas, the male subgroup was not ($p = 0.4$); Even though we acknowledge that the study was not powered to detect treatment differences in any individual subgroups and the p-values depend on the size of the subgroup, the observed response rate differences between the Linzess and placebo appear to be quite different between males and females as well; Female patients appear to have larger effect than male patients have. No other major issues were encountered during the review of this NDA.

In conclusion, from the statistical standpoint, data of Study MCP-103-3093 support statistically significant superiority of Linzess' 72 ug to Placebo for the primary efficacy endpoint, i.e., 12-week Overall Responder for complete spontaneous bowel movement (CSBM). In other words, the efficacy of oral Linzess' 72 ug for the indication of (CIC) in adults has been demonstrated.

2. INTRODUCTION

LINZESS® (linaclotide; henceforth termed linaclotide) is an orally administered therapeutic agent approved by the FDA for the treatment of adult patients with chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). Currently, the drug product is supplied as hard gelatin capsules as 145 ug strength for patients with CIC.

On March 25, 2016 Forest Laboratories, Inc. and Ironwood Pharmaceuticals, Inc. submitted NDA 202-811 jointly for LINZESS (linaclotide) 72 ug Capsules as an orally administered treatment for adult patients with chronic idiopathic constipation (CIC).

The submission includes clinical study report for a phase 3, randomized, double-blind, placebo-controlled (total of three arms; Linaclotide 72 ug, Linaclotide 145 ug and placebo), parallel-group safety and efficacy trial (Study # MCP-103-309). The duration of the study is 12 weeks.

2.1 Data Sources

The submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets (ADaM) were submitted. All data were supplied electronically by the applicant as SAS transport files and can be found in the CDER electronic document room (EDR):

[\\CDSESUB1\evsprod\NDA202811\202811.enx](#)

3. STATISTICAL EVALUATION

3.1 Description of Study (MCP-103-309)

(Descriptions in this section are extracted from the sponsor's clinical study report)

Study Objective

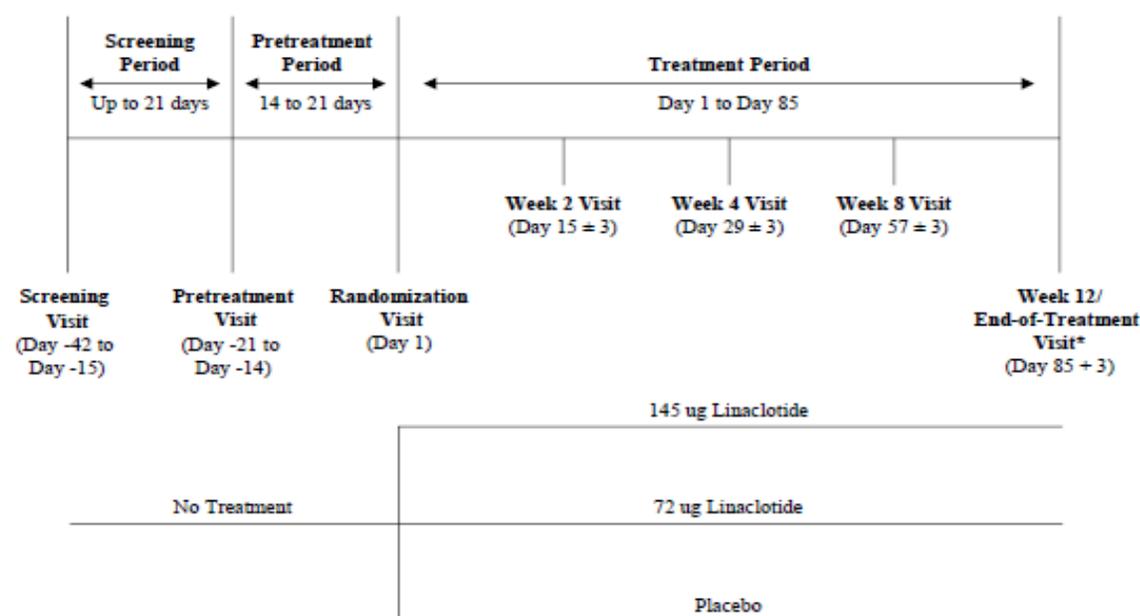
The primary objective of this trial was to determine the efficacy and safety of linaclotide 72 ug administered once daily to patients with chronic idiopathic constipation (CIC).

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, 12-week trial, consisting of 3 distinct periods as illustrated in the figure below.

Patients were stratified by baseline SBM frequency (i.e., those with > 1 SBM/week and those with ≤ 1 SBM/week) and were randomized to treatment through a central randomization.

Figure 1: Study Process



Note: there is no Day 0

* This visit represents the end of the study

Males and females aged 18 years and older were included if they met the following criteria for CIC (adapted from the Rome III Criteria for Functional Constipation):

They reported < 3 SBMs per week and reported 1 or more of the following symptoms during the 3 months before the diagnosis with the onset at least 6 months before the diagnosis: (a) straining during $\geq 25\%$ of BMs, (b) lumpy or hard stools during $\geq 25\%$ of BMs, and (c) a sensation of incomplete evacuation during $\geq 25\%$ of BMs.

Patients meeting these criteria were eligible, if during the 14-day Pretreatment Period, they reported < 3 complete SBMs (CSBMs are SBMs accompanied by patient self-reporting a feeling of complete evacuation) per week and ≤ 6 SBMs per week and were compliant with IVRS completion (i.e., they provided adequate responses on at least 10 days).

Patients were excluded for any of the following reasons: (1) they reported loose (mushy) stools in the absence of any laxative, suppository, enema, or prohibited medicine for > 25% of their BMs during the 12 weeks before the Screening Visit; (2) they met the Rome III criteria for irritable bowel syndrome; (3) during the Pretreatment Period, they reported a Bristol Stool Form Scale (BSFS) score of 7 for any SBM or a BSFS score of 6 for more than 1 SBM; (4) Patient used Rescue Medicine (bisacodyl tablet or suppository) or any other laxative, suppository, or enema, on the calendar day before or the calendar day of the start of the Treatment Period (i.e. The Randomization Visit).

Changes in the Conduct of the Trial or Planned Analyses

The following changes were implemented during the protocol stage of the trial and before the data unblinding. However, no protocol amendment regarding reportable deviations as defined by the IRB was implemented before it was approved by the IRB and the signature page, signed by the investigator, had been received by Ironwood or designee. Deviation from the protocol was permitted only if absolutely necessary for the safety of the patients and was to be immediately reported to Ironwood or designee:

- Addition question of SBM baseline frequency was asked to patients at the Randomization Visit.
- Clarification to Inclusion #3, Inclusion #8, and Exclusion #17.
- Analysis by baseline SBM stratum was added for key efficacy and safety measures.
- CSBM responders for each month were added as secondary efficacy parameters.
- The 4-step serial-gatekeeping (SGP) procedure was updated to a 5-step SGP procedure to include the additional secondary parameters and to modify the testing sequence of the secondary efficacy parameters.
- The list of additional efficacy parameters was revised.
- Sensitivity analyses for missing data were added for the primary and secondary efficacy parameters.
- Various administrative changes

Primary and Secondary Efficacy Endpoints

The primary efficacy parameter was 12-week complete spontaneous bowel movement (CSBM) overall responder.

A 12-week CSBM overall responder was defined as a patient who was a CSBM weekly responder for at least 9 of the 12 weeks of the treatment period. A CSBM weekly responder for a treatment period week was a patient who had a CSBM weekly frequency rate that was 3 or greater and increased by 1 or more from baseline based on a minimum of 4 complete IVRS calls for that week. If a patient did not have at least 4 complete IVRS calls for a particular treatment period week, the patient was not considered a CSBM weekly responder for that week. If a patient prematurely discontinued from the trial such that the patient's final treatment period week contained fewer than 4 days, the patient was not considered a CSBM weekly responder for that week or the subsequent missed weeks of the treatment period.

Secondary Efficacy Parameters were:

- Change from baseline in 12-week CSBM Frequency Rate
- Change from baseline in 12-week SBM Frequency Rate
- Change from baseline in 12-week Stool Consistency
- Change from baseline in 12-week Straining
- 12 week CSBM Overall Responder within the Baseline SBM Weekly Frequency > 1 Stratum
- Month 1 CSBM Responder
- Month 2 CSBM Responder
- Month 3 CSBM Responder
- Change from baseline in 12-week Abdominal Bloating
- Change from baseline in 12-week Abdominal Discomfort

3.2 Statistical Analysis Plan

Baseline values for efficacy parameters were derived from the IVRS daily diary collected in the Pretreatment Period, specifically the period of time from 14 days prior to the day of randomization up to the time of randomization. The baseline CSBM and SBM weekly rates were derived based on the number of CSBMs and SBMs a patient had during this period.

Baseline stool consistency and straining were calculated as the average of the non-missing values from the SBMs reported by the patient during this period. A patient's baseline stool consistency and straining could not be assessed if the patient did not have at least 1 SBM during the Pretreatment Period. Patients with missing baseline stool consistency were excluded from stool consistency analyses that involved change from baseline. Similarly, patients with missing baseline straining were excluded from straining analyses that involved change from baseline.

Determination of Sample Size

According to the Sponsor, the previously conducted Phase 3 trials of similar design and similar populations had shown a 12-week CSBM Overall Responder Rate of 3.4% to 7.6% in the placebo group and 15.5% to 20.3% in the linaclotide 145 ug group. Given the reduced linaclotide dose (72 ug) in this trial, a conservative approach was taken and a responder rate of 7.6% for placebo and 15.5% for linaclotide 72 ug was assumed for the purpose of planning the sample size for this trial. With these assumptions, a sample size of 400 patients per group was considered adequate for 93% power to detect the difference between linaclotide 72 ug and placebo in 12-week CSBM Overall Responder Rate at a 2-sided significance level of 0.05 using a Fisher's Exact test. Therefore, the number of subjects planned to be randomized into the trial was approximately 1,200 patients total (400 patients in the linaclotide 72 ug group, 400 patients in the linaclotide 145 ug group and 400 patients in the placebo group).

However, the actual number of subjects who were analyzed and were included in the Intent-to-Treat (ITT) population was 1223 (411 patients in the linaclotide 72 ug group, 411 patients in the linaclotide 145 ug group, and 401 patients in the placebo group).

3.3 Efficacy Analysis

Analysis Population

The Intent-to-treat (ITT) Population consisted of all randomized patients who received at least one dose of double-blind study drug. Efficacy analyses were based on the ITT Population, in which patients were evaluated according to the treatment group to which they were assigned at randomization.

Primary Efficacy Analysis

Corresponding with the primary objective of the trial, which was to determine the efficacy and safety of linaclotide 72 ug administered once daily to patients with CIC, the primary inference for hypothesis testing was the treatment difference between the placebo group and the linaclotide 72 ug group on the 12-week CSBM Overall Responder rate.

The primary efficacy analysis was conducted by employing a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by baseline SBM weekly frequency stratum (> 1 versus ≤ 1) and geographical region.

In a communication with the Sponsor (Serial # 0437 dated 6/30/2015), the statistical review of the protocol (Wen Jen Chen, Ph.D.) had recommended to the Sponsor to use an EXACT test since having two stratifying factors (a total of ten stratification levels) which will result in small numbers of observations in each cell: *"This will produce ten stratification levels induced by the combination of the two factors. Consequently, small numbers of observations (close to zero) may occur in cells, and the asymptotic results for the test statistics may be biased. Therefore, we recommend that you perform Exact CMH test stratified by baseline SBM stratum and geographic region as the primary analysis method."*

The null hypothesis was that there was no difference between the placebo and linaclotide 72 ug dose groups in the proportion of 12-week CSBM Overall Responders; rejection of the null hypothesis ($p \leq 0.05$) was evidence that the linaclotide 72 ug group had a higher (or lower) responder rate than the placebo group.

Secondary Efficacy Analyses

For each of the above change-from-baseline secondary efficacy parameters, the linaclotide 72 ug group was compared with the placebo group using an analysis of covariance (ANCOVA) model with fixed effect terms for treatment group, baseline SBM weekly frequency stratum, and geographical region and the corresponding baseline value as a covariate. The ANCOVA model included patients in all 3 treatment groups and the pairwise comparison between linaclotide 72 ug and placebo treatment was conducted by employing least squares (LS) means.

In addition, corresponding with the secondary objective of the study to evaluate the efficacy and safety of linaclotide 72 ug in CIC patients with more frequent SBMs at baseline, comparison between the linaclotide 72 ug group and the placebo group on the primary efficacy parameter (12-week CSBM Overall Responder) within the baseline SBM weekly frequency > 1 stratum was conducted by employing a 2-sided CMH test stratified by geographical region.

Lastly, for each of the monthly CSBM Responder parameters, the proportion of responders in the linaclotide 72 ug group was compared with the proportion of responders in the placebo group using the same methods as the primary efficacy analysis

Controlling for Multiplicity

The overall family-wise Type I error rate for the comparisons of the linaclotide 72 ug dose versus placebo for the primary and the secondary efficacy parameters was controlled at the $\alpha=0.05$ level by employing a **5-step serial gate-keeping MCP** as described below. Following this MCP, if the primary inference between the placebo group and the linaclotide 72 ug group in the overall patient population reached statistical significance ($\alpha = 0.05$) then the linaclotide 72 ug dose was considered efficacious and the MCP moved to the next step; otherwise, testing of the 72 ug dose was stopped.

For intermediate steps that include multiple parameters, if all the individual hypotheses within the step were statistically significant ($\alpha = 0.05$), then the MCP moved to the next step; otherwise the testing procedure was halted and the hypotheses tested in the current step as well as all subsequent steps were considered not statistically significant. If the procedure reached the last step, Holm's stepwise multiple comparison test method was employed to control the Type I error rate for the multiple parameters within this last step ($\alpha=0.05$).

All hypothesis tests were 2-sided.

- Step 1 tested the primary efficacy parameter, 12-week CSBM Overall Responder, for the linaclotide 72 ug group versus the placebo group at $\alpha = 0.05$.

- Step 2 tested the following 4 secondary efficacy parameters using the intersection-union test method for the linaclotide 72 ug group versus the placebo group at an overall $\alpha = 0.05$. That is, each of the 4 parameters was tested at $\alpha = 0.05$ and all 4 tests were considered not statistically significant if any 1 of the 4 null hypotheses was not rejected.
 - Change from baseline in 12-week CSBM Frequency Rate
 - Change from baseline in 12-week SBM Frequency Rate
 - Change from baseline in 12-week Stool Consistency
 - Change from baseline in 12-week Straining

- Step 3 tested the primary efficacy parameter, 12-week CSBM Overall Responder, within a pre-specified stratum defined as patients reporting baseline SBM weekly frequency > 1 for the linaclotide 72 ug group versus the placebo group at $\alpha = 0.05$.

- Step 4 tested the following 3 additional secondary efficacy parameters using the inter-section-union test method for the linaclotide 72 ug group versus the placebo group at an overall $\alpha = 0.05$. That is, each of the 3 parameters was tested at $\alpha = 0.05$ and all 3 tests were considered not statistically significant if any 1 of the 3 null hypotheses was not rejected.
 - Month 1 CSBM Responder
 - Month 2 CSBM Responder
 - Month 3 CSBM Responder

- Step 5 tested the remaining 2 secondary efficacy parameters for the linaclotide 72 ug group versus the placebo group using Holm’s stepwise multiple comparison test method at an overall $\alpha = 0.05$.

- Change from baseline in 12-week Abdominal Bloating
- Change from baseline in 12-week Abdominal Discomfort

Pooling of Trial Centers

Because of the potential of many trial centers’ to have a small number of patients, the centers were pooled by the following 5 geographic regions: Northeast, Southeast, Midwest, Southwest, and West. All analyses using trial center used this 5-category pooled trial center variable.

Table 1: Definition of Geographic Regions

<i>Northeast</i>	<i>Southeast</i>	<i>Midwest</i>	<i>Southwest</i>	<i>West</i>
CT	AL	IA	AZ	CA
DE	AR	IL	NM	CO
MA	FL	IN	OK	ID
MD	GA	KS	TX	MT
ME	KY	MI		NV
NH	LA	M		OR
NJ	MS	MO		UT
NY	NC	ND		WA
PA	SC	NE		WY
RI	TN	OH		
VT	VA	SD		
	WV	WI		

Among the 5 geographic regions, the greatest number of patients were randomized to sites in the Southeast (744 patients), while the least number of patients were randomized to sites in the Midwest (63 patients).

Handling of Missing IVRS Data and Analysis Methods and Data Handling Conventions

All efficacy analyses were based on the ITT Population.

Baseline values for efficacy parameters were derived from the Interactive Voice Response System (IVRS) daily diary collected in the Pretreatment Period, specifically the period of time from 14 days prior to the day of randomization up to the time of randomization. The baseline CSBM and SBM weekly rates were derived based on the number of CSBMs and SBMs a patient had during this period.

In the IVRS system, for each BM and rescue medicine use reported, the patient was asked whether the BM or rescue medicine use occurred “today” or “yesterday.” However, missing values for these and other IVRS fields are anticipated because of missing and incomplete IVRS daily diary calls. The following conventions were followed in the event of missing data:

Gaps in the Interactive Voice Response System Diary Data:

If a patient does not call the IVRS system every day, there will be gaps in the data. For example, consider the scenario in which a patient calls into the IVRS on Monday at 8:00 PM, skips the Tuesday call, and then calls in on Wednesday. During the Wednesday call, the patient will only be

allowed to report rescue medicine use and BMs since 12:01 AM on Tuesday. Thus, there will be no IVRS data for the period from 8:00 PM Monday night until midnight.

There will be no adjustments for these gaps in the IVRS data for the efficacy data analyses using an observed-cases approach. Effectively, this means that analyses will assume that no rescue medicine use or BMs occurred during these gaps.

ITT Population patients with no post-baseline BM evaluations while on study drug were considered to have zero SBMs and CSBMs between the first and last dose date of study drug.

For weekly responder parameters based on daily IVRS assessments, a patient with fewer than 4 complete IVRS calls during an analysis week was not considered a responder for that week.

Under the Last Observation Carried Forward (LOCF) approach, if a patient had < 4 complete IVRS calls for any of the 12 Treatment Period weeks, the patient's responder status for that week was imputed by the value of the patient's responder status from the previous week during the Treatment Period. If no previous week responder status existed within the Treatment Period, then the patient was considered a non-responder for that week. Thus, the 12-week CSBM Overall Responder under the LOCF approach was a patient who was a CSBM weekly responder for at least 9 of the 12 weeks of the Treatment Period, using the above LOCF approach for determining a weekly responder.

Sensitivity Analyses of the Primary Efficacy Parameter

An LOCF approach was used to impute missing post-baseline values as a sensitivity analysis for the primary efficacy parameter. The potential impact of missing IVRS data related to the primary efficacy parameter on the estimates of treatment effect was assessed using alternative statistical methods.

The same CMH test used for the primary efficacy analysis was applied in these sensitivity analyses. In order to characterize the extent of missing data associated with the primary efficacy parameter, the number and percentage of patients with < 4 complete IVRS calls were presented by treatment group for the ITT Population for each week of the Treatment Period.

Baseline values for patient symptom severity parameters (e.g., abdominal discomfort, abdominal bloating, abdominal pain, and constipation severity) were the average of the non-missing severity scores reported during this period.

3.4 Study Results

Patient Disposition and Discontinuation

A total of 2244 patients were screened; 1223 were randomized and 1021 were not randomized (478 patients were screen failures and 543 patients were pretreatment failures).

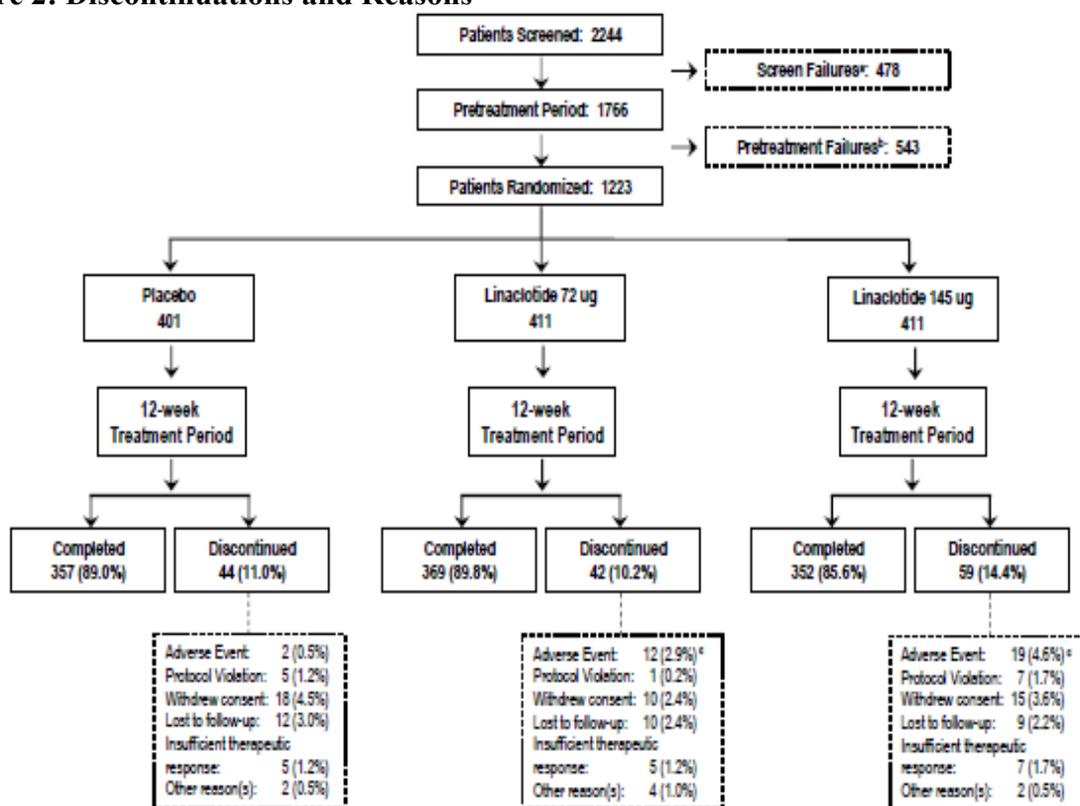
Of the 1223 patients who provided informed consent, successfully completed the screening and pretreatment periods, and were randomized to treatment, 1078 (88.1%) completed the Treatment Period.

Table 2: Analysis Populations

Patient Population	Placebo	Linaclotide		Total
		72 ug	145 ug	
Randomized Population	401	411	411	1223
Safety Population	401	411	411	1223
ITT Population	401	411	411	1223
ITT Population by Geographic Region ^a :				
Southeast	247	254	243	744
West	60	57	65	182
Southwest	49	41	52	142
Northeast	25	36	31	92
Midwest	20	23	20	63

Source: Sponsor's Study Report

Figure 2: Discontinuations and Reasons



Source: Sponsor's Study Report

Figure 2 shows that a total of 44 out of 401(11%) subjects in the Placebo arm, 42 out of 411 (10%) subjects in the 72 ug arm and a total of 59 out of 411 subjects (14%) in the 145 ug discontinued the study for different reasons. Even though these dropout rates seem to be high, but, they were not statistically different among all the three arms (p>0.1).

We should note, however, that the Sponsor has reported their final results based on the worst case scenario, where they have accounted all the withdrawals as failures.

To further In addition, in this review, as a sensitivity analyses, we re-analyzed the data based on completers only and it is shown in Section 3.4 of this review.

Demographics and Baseline Characteristics

The majority of patients were Caucasian (71.0%) and female (77.0%). Hispanic or Latino ethnicity was reported by 43.2% of patients. The treatment groups were generally balanced with respect to demographics and other baseline characteristics. Mean patient age for all patients was 46.0 years; means for individual treatment groups were 45.2 years for the placebo group, 45.8 years for the linaclotide 72 ug group, and 46.8 years for the linaclotide 145 ug group. Patients \geq 65 years of age composed 9.6% of the Safety Population; Black or African American patients composed 23.6%.

Table 3 provides a summary of the demographic and baseline characteristics for the Safety Population. Demographic and baseline characteristics results were identical for the ITT Population.

Table 3: Demographic and Baseline Characteristics Results

Demographic Characteristic	Placebo (N=401)	Linaclotide		Total (N=1223)
		72 ug (N=411)	145 ug (N=411)	
Age, years				
Mean (SD)	45.2 (14.7)	45.8 (14.3)	46.8 (14.0)	46.0 (14.3)
Median (Min, Max)	46.0 (18, 83)	46.0 (18, 90)	47.0 (18, 86)	46.0 (18, 90)
Age, n (%)				
18 to < 40 years	142 (35.4)	140 (34.1)	128 (31.1)	410 (33.5)
40 to < 65	220 (54.9)	235 (57.2)	240 (58.4)	695 (56.8)
\geq 65 years	39 (9.7)	36 (8.8)	43 (10.5)	118 (9.6)
Gender, n (%)				
Female	316 (78.8)	312 (75.9)	314 (76.4)	942 (77.0)
Male	85 (21.2)	99 (24.1)	97 (23.6)	281 (23.0)
Race, n (%)				
Caucasian	276 (68.8)	298 (72.5)	294 (71.5)	868 (71.0)
Non-Caucasian	125 (31.2)	113 (27.5)	117 (28.5)	355 (29.0)
Black/African American	102 (25.4)	93 (22.6)	94 (22.9)	289 (23.6)
Asian	18 (4.5)	14 (3.4)	16 (3.9)	48 (3.9)
Other	5 (1.2)	6 (1.5)	7 (1.7)	18 (1.5)
Ethnicity, n (%)				
Hispanic or Latino	175 (43.6)	178 (43.3)	175 (42.6)	528 (43.2)
Not Hispanic or Latino	226 (56.4)	233 (56.7)	236 (57.4)	695 (56.8)
Baseline SBM Stratum, n (%)				
\leq 1 SBM/week	175 (43.6)	167 (40.6)	176 (42.8)	518 (42.4)
> 1 SBM/week	226 (56.4)	244 (59.4)	235 (57.2)	705 (57.6)
Weight, kg				
Mean (SD)	80.3 (19.7)	79.7 (18.1)	80.1 (18.8)	80.0 (18.8)
Median (Min, Max)	78.8 (44, 193)	78.5 (40, 141)	78.0 (45, 158)	78.3 (40, 193)
Height, cm				
Mean (SD)	165.3 (9.0)	165.8 (9.0)	165.3 (9.5)	165.5 (9.2)
Median (Min, Max)	165.0 (135, 205)	165.1 (147, 196)	165.0 (142, 201)	165.1 (135, 205)

Source: Sponsor's Study Report

Of note, the majority of subjects were female (77%). However, based on the clinical reviewer, this is similar to the general population with this disease.

Analysis of the Primary Efficacy Endpoint

Table 4 shows the baseline efficacy variables by the Sponsor.

Table 4: Sponsors' Baseline Efficacy Variables

Efficacy Parameter	Statistic	Placebo (N=401)	Linaclotide		Total (N=1223)
			72 ug (N=411)	145 ug (N=411)	
CSBM Weekly Rate	n	401	411	411	1223
	Mean (SD)	0.25 (0.48)	0.22 (0.52)	0.20 (0.44)	0.22 (0.48)
	Median	0.00	0.00	0.00	0.00
	Min, Max	0.0, 2.4	0.0, 2.9	0.0, 2.4	0.0, 2.9
SBM Weekly Rate	n	401	411	411	1223
	Mean (SD)	1.56 (1.15)	1.74 (1.42)	1.67 (1.38)	1.66 (1.33)
	Median	1.45	1.46	1.45	1.45
	Min, Max	0.0, 5.8	0.0, 6.3	0.0, 6.3	0.0, 6.3
Stool Consistency (BSFS) ^a	n	359	360	364	1083
	Mean (SD)	2.04 (1.02)	1.94 (0.93)	1.96 (0.94)	1.98 (0.96)
	Median	2.00	1.83	1.75	1.83
	Min, Max	1.0, 6.0	1.0, 6.0	1.0, 7.0	1.0, 7.0
Straining ^a	n	359	360	364	1083
	Mean (SD)	3.51 (0.88)	3.62 (0.86)	3.52 (0.82)	3.55 (0.85)
	Median	3.75	3.80	3.67	3.71
	Min, Max	1.0, 5.0	1.0, 5.0	1.0, 5.0	1.0, 5.0
Abdominal Discomfort	n	401	411	411	1223
	Mean (SD)	4.76 (2.56)	4.64 (2.74)	4.71 (2.66)	4.70 (2.65)
	Median	4.92	4.87	4.64	4.85
	Min, Max	0.0, 9.9	0.0, 10.0	0.0, 10.0	0.0, 10.0
Abdominal Bloating	n	401	411	411	1223
	Mean (SD)	5.29 (2.39)	5.24 (2.61)	5.30 (2.57)	5.27 (2.52)
	Median	5.40	5.43	5.33	5.40
	Min, Max	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0

Source: Sponsor's Study Report

Overall, the percentage of patients who were $\geq 80\%$ IVRS compliant during the 2-week Pretreatment Period was 94.8% for placebo, 96.6% for linaclotide 72 ug, and 95.9% for linaclotide 145 ug. During the 12-week Treatment Period, 70.8%, 73.2%, and 70.3% of placebo, 72 ug, and 145 ug patients had a complete IVRS call at least 80% of the time.

Table 5 shows the sponsor's analyses for the primary efficacy endpoint based on Odds Ratio.

Table 5: Sponsors' Results of the Analyses of Efficacy Variables (ITT)

Description	Placebo (N=401) n (%)	Linaclotide	
		72 ug (Primary EP) (N=411) n (%)	145 ug (N=411) n (%)
Responder	19 (4.7)	55 (13.4)	51 (12.4)
Non-Responder	382 (95.3)	356 (86.6)	360 (87.6)
Difference in Responder Rate (Linaclotide - Placebo)		8.6	7.7
Odds Ratio for Response (Linaclotide : Placebo)		3.03	2.82
95% CI for Odds Ratio		(1.76, 5.20)	(1.63, 4.90)
P-value		< 0.0001*	< 0.0001

Reviewer's Note:

The statistical reviewer confirmed the sponsor's analysis results and although the response rates are not substantially large numerically in the two active arms, however, they result in a highly statistically significant difference when compared to placebo ($p < 0.0001$). It would be a clinical judgment as to whether these numbers are clinically meaningful.

Also, it is worth pointing out that, numerically, the 72 ug has a higher response rate than the 145 ug (13.4% vs. 12.4% respectively)

Sensitivity Analyses

We should note that the Sponsor has reported their final results based on the worst case scenario, where they have accounted all the withdrawals as failures.

In addition, in this review, we re-analyzed the data based on completers only. Table 6 shows these results.

Table 6: Reviewer's Results of the Analyses of Primary Efficacy Variables (Completers)

	Placebo n=357	72 ug n=369	145 ug n=352	Overall P- Value
Response Rate	18 (5.0%)	54 (14.6%)	51 (14.5%)	<0.0001

The results were similar to that of the ITT population.

Analysis of the Secondary Efficacy Endpoint

The Sponsor has introduced several secondary efficacy endpoints:

Secondary Efficacy Parameters

- Change from baseline in 12-week CSBM Frequency Rate
- Change from baseline in 12-week SBM Frequency Rate
- Change from baseline in 12-week Stool Consistency
- Change from baseline in 12-week Straining
- 12 week CSBM Overall Responder within the Baseline SBM Weekly Frequency > 1 Stratum
- Month 1 CSBM Responder
- Month 2 CSBM Responder
- Month 3 CSBM Responder
- Change from baseline in 12-week Abdominal Bloating
- Change from baseline in 12-week Abdominal Discomfort

In this review we report the results of the first 4 parameters, only. This was agreed upon by the medical reviewer.

Table 7: Sponsor's Results of the Analyses of Secondary Efficacy Variables (ITT)

Efficacy Parameter	Placebo (N=401)	72 ug (N=411)		
Change from Baseline	LS Mean (SE)	LS Mean (SE)	LSMD (95% CI)	p-value ^d
12-week CSBM Frequency	0.884 (0.142)	1.725 (0.139)	0.841 (0.505, 1.176)	< 0.0001
12-week SBM Frequency	1.329 (0.169)	2.366 (0.166)	1.037 (0.636, 1.438)	< 0.0001
12-week Stool Consistency	1.065 (0.076)	1.693 (0.074)	0.628 (0.450, 0.806)	< 0.0001
12-week Straining	-0.789 (0.051)	-1.118 (0.050)	-0.329 (-0.449, -0.210)	< 0.0001

The results of the reviewer's analyses of the secondary endpoint variables were similar to that of the Sponsor's and were highly statistically significant (p<0.0001).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Table 8: Reviewers' Results of the Analyses of Efficacy Variables

Total	Placebo n=401		72 ug n=411	145 ug n=411
Gender				
<i>Female</i>	n=316		n=312	n=314
Response Rate	14 (4%)		45 (14%)	40 (13%)
<i>Male</i>	n=85		n=99	n=97
Response Rate	5 (6%)		10 (10%)	11 (11%)
Age Group				
<i>18 to <40</i>	n=142		n=140	n=128
Response Rate	4 (3%)		14 (10%)	9 (7%)
<i>40 to <65</i>	n=220		n=235	n=240
Response Rate	13 (6%)		36 (15%)	37 (15%)
<i>>= 65</i>	n=39		n=36	n=43
Response Rate	2 (5%)		5 (14%)	5 (12%)
Ethnic Group				
<i>Hispanic</i>	n=175		n=178	n=175
Response Rate	6 (3%)		22 (12%)	18 (10%)
<i>Non-Hispanic</i>	n=226		n=233	n=236
Response Rate	13 (6%)		33 (14%)	33 (14%)
Race				
<i>Asian</i>	n=18		n=14	n=16
Response Rate	0 (0%)		1 (7%)	1 (6%)
<i>Black</i>	n=102		n=93	n=94
Response Rate	9(9%)		12 (13%)	11 (12%)
<i>White</i>	n=276		n=298	n=294
Response Rate	9 (3%)		40 (13%)	38 (13%)

One concern was the number of female to male ratio (larger than 3:1). When the primary analysis was performed by gender, the female subpopulation was highly statistically significant ($p < 0.0001$) whereas, the male subgroup did not show statistical significance ($p = 0.4$); however, it should also be noted that the study was not powered to show statistical significance difference for efficacy by each gender individually.

Table 8 shows that subjects between the ages of 40 to 65 had a higher response rate than the other age categories for both 72 ug and 145 ug (15% for both treatment arms). Also, the non-Hispanic group had a higher response rate compared to Hispanics in both active treatment arms (14% for both groups). However, these numbers should be interpreted with caution, since the number of subjects in these categories was not similar.

Because of the potential of many trial centers' having small number of patients, the sponsor had pooled the centers by the following 5 geographic regions: Northeast, Southeast, Midwest, Southwest, and West. All analyses using trial center used this 5-category pooled trial center variable. Table 9 shows the results of efficacy for each of these regions individually.

Table 9: Reviewers' Results of the Analyses of Efficacy Variables by Region

Total	Placebo n=401	72 ug n=411	145 ug n=411
<i>Region 1 (n=92)</i>	n=25	n=36	n=31
Response Rate	1 (4%)	5 (14%)	6 (19%)
<i>Region 2 (n=744)</i>	n=247	n=254	n=243
Response Rate	12 (5%)	28 (11%)	20 (8%)
<i>Region 3 n=(63)</i>	n=20	n=23	n=20
Response Rate	3 (15%)	2 (9%)	4 (20%)
<i>Region 4 (n=142)</i>	n=49	n=41	n=52
Response Rate	1 (2%)	9 (22%)	11 (21%)
<i>Region 5 (n=182)</i>	n=60	n=57	n=65
Response Rate	2 (3%)	11 (19%)	10 (15%)

As it is seen in Table 9, Region 2 had the highest number of subjects. In addition, the response rates in all these regions were so dissimilar, ranging from the high of 22% to the low of 9% for the 72 ug arm and the high of 21% to 8% for the 145 ug treatment group.

5. SUMMARY AND CONCLUSIONS

The Sponsor conducted one phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, 12-week trial (Study MCP-103-3093) to demonstrate the effectiveness of Linzess. From the statistical standpoint, Study MCP-103-3093 showed a highly statistically significant superiority of Linzess' 72 ug to Placebo on the primary efficacy endpoint, which is the Overall Responder for the 12-week complete spontaneous bowel movement (CSBM); and therefore, can be used to support the efficacy of oral Linzess' 72 ug for the indication of Chronic Idiopathic Constipation (CIC) in adults.

After thorough review, we had a concern regarding the 3:1 randomization ratio of female to male. A total of 942 female patients vs. 281 males were randomized into the study. As a result, when the primary analysis was performed by gender, the female subpopulation showed a highly statistically significant result ($p < 0.0001$); whereas, the male subgroup did not indicate any statistical significance ($p = 0.4$). This might have been contributed to the smaller sample size for the males or could just be due to chance; nonetheless, these results should be interpreted with caution.

No other major issues were encountered during the review of this NDA.

Appendix

Sponsor's Table of Results

MCP Step Efficacy parameter	Placebo (N=401)	Linaclotide 72 ug (N=411)			MCP met?
MCP Step 1 – Primary Efficacy Parameter (ITT Population)					
Responder	n/N (%)	n/N (%)	OR ^c (95% CI)	p-value ^c	Yes/No
12-week CSBM Overall ^{a,c}	19/401 (4.7)	55/411 (13.4)	3.03 (1.76, 5.20)	< 0.0001	Yes
MCP Step 2 (ITT Population)					
Change from Baseline	LS Mean (SE)	LS Mean (SE)	LSMD (95% CI)	p-value ^d	Yes/No
12-week CSBM Frequency ^d	0.884 (0.142)	1.725 (0.139)	0.841 (0.505, 1.176)	< 0.0001	Yes
12-week SBM Frequency ^d	1.329 (0.169)	2.366 (0.166)	1.037 (0.636, 1.438)	< 0.0001	Yes
12-week Stool Consistency ^d	1.065 (0.076)	1.693 (0.074)	0.628 (0.450, 0.806)	< 0.0001	Yes
12-week Straining ^d	-0.789 (0.051)	-1.118 (0.050)	-0.329 (-0.449, -0.210)	< 0.0001	Yes
MCP Step 3 (> 1 SBM/Week Subpopulation)					
Responder	n/N (%)	n/N (%)	OR ^e (95% CI)	p-value ^e	Yes/No
12-week CSBM Overall ^{a,c}	16/401 (7.1)	42/411 (17.2)	2.68 (1.47, 4.87)	0.0008	Yes
MCP Step 4 (ITT Population)					
Responder	n/N (%)	n/N (%)	OR ^c (95% CI)	p-value ^c	Yes/No
CSBM Month 1 ^b	25/401 (6.2)	61/411 (14.8)	2.58 (1.58, 4.20)	< 0.0001	Yes
CSBM Month 2 ^b	38/401 (9.5)	77/411 (18.7)	2.15 (1.42, 3.26)	0.0002	Yes
CSBM Month 3 ^b	57/401 (14.2)	83/411 (20.2)	1.49 (1.03, 2.17)	0.0342	Yes
MCP Step 5 (ITT Population)					
Change from Baseline	LS Mean (SE)	LS Mean (SE)	LSMD (95% CI)	p-value ^d	Yes/No
Abdominal Bloating ^d	-1.052 (0.097)	-1.372 (0.095)	-0.319 (-0.548, -0.090)	0.0063	Yes
Abdominal Discomfort ^d	-1.146 (0.090)	-1.323 (0.089)	-0.178 (-0.391, 0.036)	0.1028	No

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/s/

SHAHLA S FARR
11/10/2016

YEH FONG CHEN
11/10/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202811/S-010	Submission Date(s): 03/25/2016
Brand Name	Linzess
Generic Name	Linaclotide
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Forest Laboratories, Inc.
Relevant IND(s)	63290
Submission Type; Code	Efficacy Supplement
Formulation; Strength(s)	72 µg capsules
Indication	Chronic Idiopathic Constipation (CIC)

Recommendation: sNDA 202811 submitted 03/25/2015 is acceptable from a Clinical Pharmacology perspective. There are no pending issues, or post-marketing proposals.

Background: Linaclotide, a 14-amino acid peptide guanylate cyclase-C (GC-C) agonist, is currently approved for the treatment of chronic idiopathic constipation (CIC) at a dose of 145 µg and for the treatment of irritable bowel syndrome with constipation (IBS-C) at a dose of 290 µg. At clinically relevant doses, the parent drug or its active metabolite were not observed in the systemic circulation.

Current submission: The sponsor has submitted an efficacy supplement to support adding a lower dose of 72 µg to the labeling for CIC. In this regard the current sNDA contains efficacy data for this dose, as well as CMC information. The sponsor has conducted a 12-week, randomized, placebo-controlled, phase 3 clinical trial MCP-103-309 as a confirmatory trial to support the effectiveness of linaclotide 72 µg. Supporting information is cited from the following previously submitted/reviewed studies: MCP-103-303, and LIN-MID-01, the phase 3 CIC registration trials for linaclotide 145 µg, as well as MCP-103-201, a 4-week, phase 2b dose-range finding trial in CIC, which included the 72 µg dose proposed.

Clinical Pharmacology: There was no new Clinical Pharmacology information in this sNDA. The supporting dose-ranging study MCP-103-201 was reviewed during the original approval cycle by OCP. Please refer to Clinical Pharmacology review dated 04/06/2012 in DARRTs for additional information on this dose-ranging trial. The Division of Pharmacometrics in OCP has looked into available dose-response information on request from clinical reviewers. Please refer to DARRTs for a separate review in this regard by Drs. Jee Eun Lee and Nitin Mehrotra.

Labeling: Minor labeling revisions were carried out in this review cycle. Please refer to the final label once available.

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/s/

SANDHYA K APPARAJU
11/21/2016

SUE CHIH H LEE
11/21/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 7, 2016

To: Cheronda Cherry-France, RN, BSN, MHA
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

Subject: NDA # 202811 /S-010 – LINZESS (linaclotide) capsules, for oral use

Reference is made to DGIEP's consult request dated May 5, 2016, requesting review of the proposed Package Insert (PI), Medication Guide (MG), and Carton/Container labeling for LINZESS (linaclotide) capsules, for oral use.

OPDP has reviewed the proposed PI entitled, "NDA 202811.s.10 proposed draft-labeling w. DGIEP Edits Sent 11.30.2016.docx" that was sent via e-mail from DGIEP to OPDP on November 30, 2016. OPDP's comments on the proposed PI and MG are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling submitted by the sponsor on October 21, 2016, and located at <\\CDSESUB1\evsprod\NDA202811\202811.enx>. OPDP has no comments at this time on the proposed Carton/Container labeling.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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ADEWALE A ADELEYE
12/07/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 2, 2016

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Focused Review of Patient Labeling: Medication Guide
(MG)

Drug Name (established name): LINZESS (linaclotide)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 202811

Supplement Number: S-010

Applicant: Forest Laboratories, Inc.

1 INTRODUCTION

On March 25, 2016 Forest Laboratories, Inc. submitted for the Agency's review an Efficacy Supplemental New Drug Application (sNDA) 202811/S-010 for LINZESS (linaclotide) capsules, for oral use. The Applicant is seeking marketing approval for a 72 µg dose of LINZESS as an orally administered treatment for adult patients with chronic idiopathic constipation (CIC).

LINZESS (linaclotide) capsules, for oral use was approved on August 30, 2012 and is indicated in adults for the treatment of:

- Irritable bowel syndrome with constipation (IBS-C)
- Chronic idiopathic constipation (CIC)

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on May 5, 2016 for DMPP to review the Applicant's proposed Medication Guide (MG) for LINZESS (linaclotide) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft LINZESS (linaclotide) capsules, for oral use MG received on March 25, 2016 and received by DMPP on November 30, 2016.
- Draft LINZESS (linaclotide) capsules, for oral use Prescribing Information (PI) received on March 25, 2016, revised by the review division throughout the review cycle, and received by DMPP on November 30, 2016.
- Approved labeling for LINZESS (linaclotide) capsules, for oral use dated August 31, 2016.

3 REVIEW METHODS

In our focused review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.

- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NYEDRA W BOOKER
12/02/2016

MARCIA B WILLIAMS
12/02/2016

**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRICS REVIEW**

NDA: 202811	Submission Date: March 25, 2016
Generic Name	Linaclotide
Reviewer	Jee Eun Lee, Ph.D.
Secondary Reviewer	Nitin Mehrotra, Ph.D.
ORM division	OND/ DGIEP
Sponsor	Ironwood Pharmaceuticals
Formulation; Strength(s)	Capsule; 72, 145 mcg
Indication	Treatment of adults with Chronic idiopathic constipation (CIC)

1. Introduction

This review is a brief memorandum for sNDA202811 for treatment of CIC with 72 mcg QD as an additional dose.

Linaclotide (Linzess®) is a guanylate cyclase-C agonist that was approved in 2012 for treatment of irritable bowel syndrome with constipation (IBS-C) at a dose of 290 mcg and chronic idiopathic constipation (CIC) at a dose of 145 mcg. The sponsor received medical inquiries from practicing physicians regarding the availability of linaclotide doses lower than the commercially available 145 mcg dose for the treatment of CIC, which was 72 mcg. Thus, the sponsor evaluated the efficacy and safety of a lower dose of linaclotide in a Phase 3 confirmatory trial in CIC patients (MCP-103-309, Study 309). Based on the results obtained from the Phase 3 trial and the previously conducted Phase 2 dose-ranging study (MCP-103-201, Study 201), the sponsor proposed to recommend 72 mcg QD dose for the CIC additionally to the approved dose of 145 mcg QD.

The baseline characteristics of patient population between MCP-103-309 and MCP-103-201 are different in terms of baseline CSBM and SBM frequency rates, Bristol Stool Form Scale (BSFS) score and straining score. Thus, the review performed analyses to evaluate the effect of baseline characteristics on dose-response relationship of linaclotide.

2. Background

In Study 309, the safety and efficacy of linaclotide 72 mcg and 145 mcg was evaluated along with placebo in a total of 1223 patients for 12 weeks. The dose ranging study (Study 201) evaluated the efficacy and safety of linaclotide 72 mcg, 145 mcg, 290 mcg and 579 mcg along with placebo in total of 307 subjects for 4 weeks. The primary outcome of interest was complete spontaneous bowel movement (CSBM) and spontaneous bowel movement (SBM). The primary endpoint in Phase 3 was 12-week CSBM Overall Responder (CSBM weekly responder for ≥ 9 of the 12 weeks of treatment) and that in the Phase 2 study was CSBM 75% responder (CSBM weekly responder for ≥ 3 of the 4 weeks of treatment). A brief comparison of the study design of the two studies is shown in Figure 1.

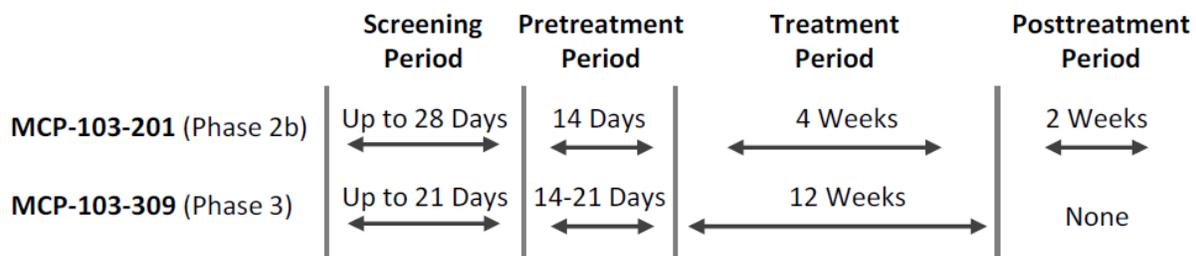


Figure 1. Study Design of Study 201 and Study 309

(Source: Sponsor's report SCE, Figure 1-1, page 13)

The efficacy results obtained from the Phase 3 and Phase 2 studies are summarized in Table 1 and Table 2.

Table 1. Summary of Efficacy in Study 309

Description	Placebo (N = 401)	Linaclotide	
		72 ug (Primary Parameter) (N = 411)	145 ug (Additional Parameter) (N = 411)
Responder, n (%)	19 (4.7)	55 (13.4)	51 (12.4)
Difference in Responder Rate (Linaclotide - Placebo)		8.6	7.7
Odds Ratio for Response (Linaclotide : Placebo)		3.0	2.8
95% CI for Odds Ratio		(1.8, 5.2)	(1.6, 4.9)
P-value		< 0.0001	0.0001

(Source: Sponsor's report SCE, Table 3-5, page 29)

Table 2. Summary of Efficacy in Study 201

<i>Parameter</i>	<i>Placebo</i> (<i>N</i> = 68)	<i>Linaclootide</i>			
		<i>72 ug</i> (<i>N</i> = 59)	<i>145 ug</i> (<i>N</i> = 56)	<i>290 ug</i> (<i>N</i> = 62)	<i>579 ug</i> (<i>N</i> = 62)
SBM 75% Responder, n (%)	21 (30.9)	35* (59.3)	31* (55.4)	38** (61.3)	42*** (67.7)
CSBM 75% Responder, n (%)	5 (7.4)	11 (18.6)	15* (26.8)	21** (33.9)	18* (29.0)

*p ≤ 0.05; **p < 0.001; ***p < 0.0001

(Source: Sponsor's report SCE, Table 2-2, page 22)

3. Summary of Findings

Dose-response for overall population

Dose-response relationships for CSBM Overall 75% Responder were observed in the dose ranging study (Study 201) up to 290 mcg linaclootide, although the difference in 72 mcg and 145 mcg doses in Study 309 was not observed (Figure 2). Therefore, we investigated if the difference in baseline characteristics of population might have influenced this finding. The mean (SD) baseline SBM was 1.65 (0.32) per week for patients in Study 309 and 2.22 (1.49) per week for those in Study 201. Thus, subgroup analyses by baseline SBM rate were performed for data from the two studies.

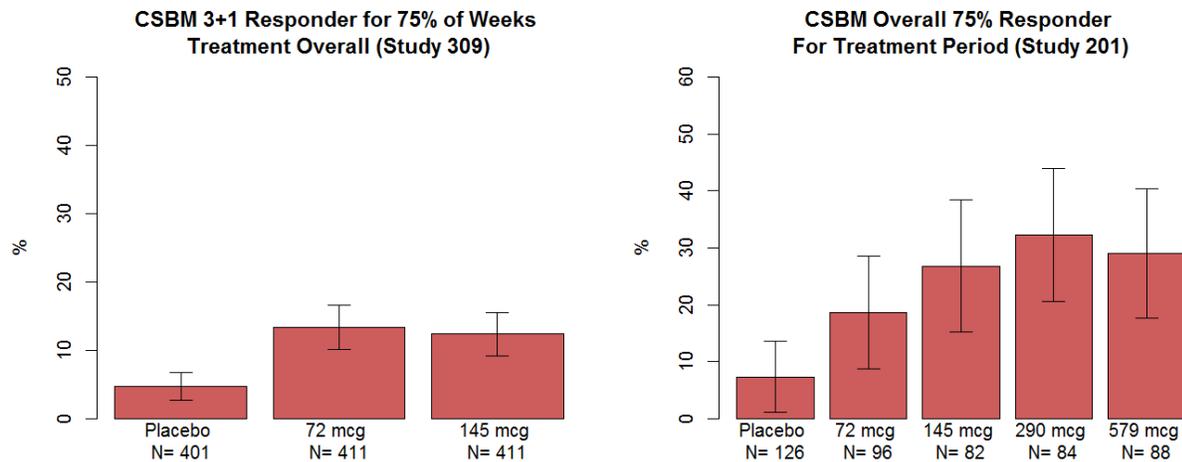


Figure 2. Dose-Response for Primary Efficacy for Study 309 and Study 201

Dose-response by baseline SBM rate

The subgroup analysis for patients with baseline SBM rate lower than median and those with higher than median was performed. Although the rate for CSBM responder for 75% of weeks treatment in patients with Low Baseline SBM rate group (mean baseline SBM rate was 0.66 /week) was lower than those with High Baseline SBM rate group (mean baseline SBM rate was 2.59 /week), the 72 mcg dose QD showed similar response compared to 145 mcg in both baseline SBM rate groups (Figure 3).

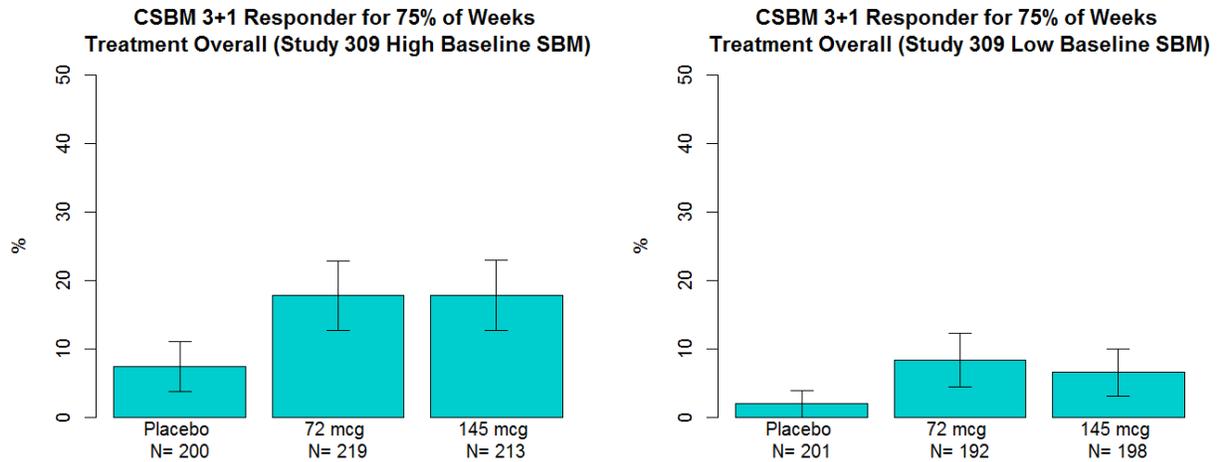


Figure 3. Dose-Response for CSBM 3+1 Response for 75% of Weeks Treatment Overall by Baseline SBM Rate (< median SBM vs. ≥ median SBM, Study 309)

Similar analysis was performed for the primary CSBM responder rates in the Phase 2 study. The response profiles in Low Baseline SBM rate group (mean baseline SBM rate was 1.07 /week) and High Baseline SBM rate group (mean baseline SBM rate was 3.38 /week) appear to be different. The 72 mcg dose QD showed lower response compared to 145 mcg in Low baseline SBM rate group while there appears to be no trend of dose-response in the high baseline SBM rate group (Figure 4).

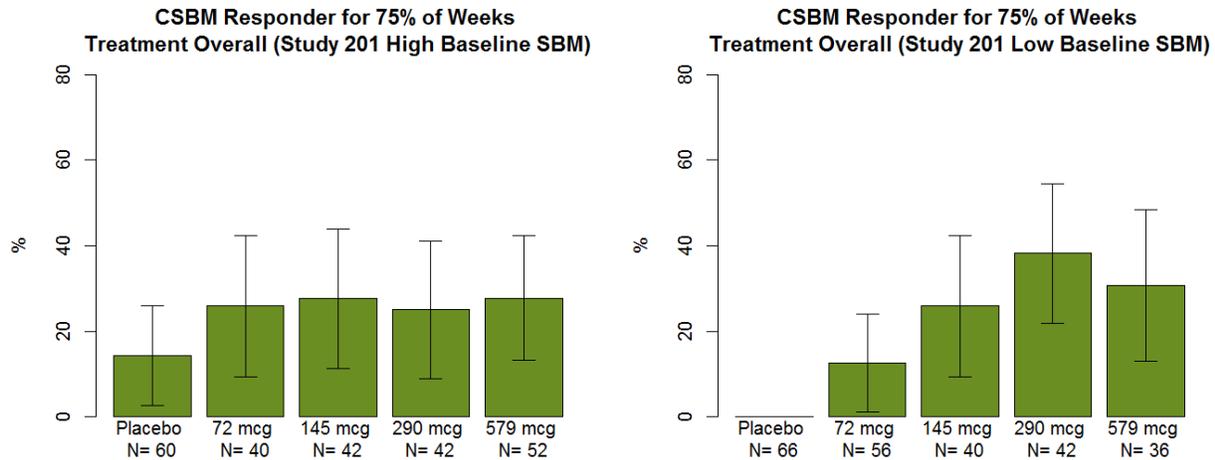


Figure 4. Dose-Response for CSBM Responder for 75% of Weeks Treatment Overall (< median SBM vs. \geq median SBM, Study 201)

Since the majority of patients (931 out of 1223 in Study 309 and 188 out of 307 in Study 201) had CSBM rate of 0 at baseline, the difference in SBM (>1 SBM/week and ≤ 1 SBM/week) might have influenced the different dose-response in sicker patients i.e. patients with ≤ 1 SBM/week. Furthermore, the efficacy of linaclotide 72 mcg was evaluated in subpopulations defined as less or more symptomatic by baseline SBM frequency rate (>1 SBM/week (less symptomatic) and ≤ 1 SBM/week (more symptomatic)), stratified by this baseline SBM frequency rate upon randomization.

As shown in Figure 5, the response rate between 72 mcg QD and 145 mcg QD were similar for both patients with > 1 baseline SBM/week and that in those with ≤ 1 baseline SBM/week with data obtained from Study 309. However, the response rates across between 72 mcg QD and 145 mcg QD were quite different by baseline SBM rate with data obtained from Study 201 (Figure 6). Since the Study 309 was stratified by the baseline SBM, more number of patients with ≤ 1 baseline SBM/week were included in Phase 3 study (N=170 for 72 mcg, N=174 for 145 mcg) than Phase 2 study (N=15 for 72 mcg, N=15 for 145 mcg). Moreover, the dose-response response with the Phase 2 data was not consistent (response with 290 mcg was lower than that with 145 mcg), while the dose-response relationship in a subgroup of patients in study 309 whose baseline CSBM was 0 appear to be consistent in the dose-response relationship in all patients (Figure 7). Thus, the subgroup analysis with Phase 3 data is considered more reliable.

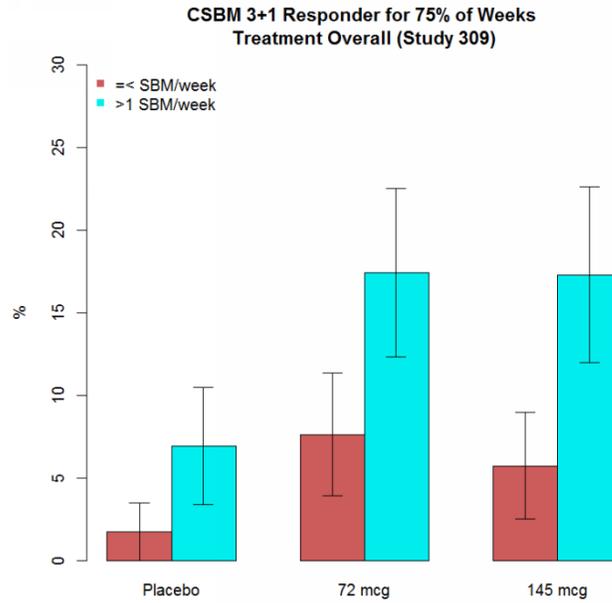


Figure 5. Dose-Response for CSBM 3+1 Response for 75% of Weeks Treatment Overall by Baseline SBM Rate (>1 SBM/week vs. ≤1 SBM/week, Study 309)

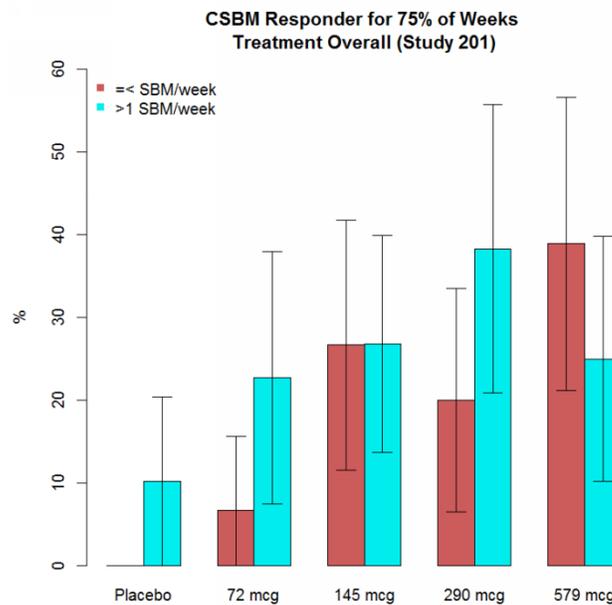


Figure 6. Dose-Response for CSBM Responder for 75% of Weeks Treatment Overall by Baseline SBM Rate (>1 SBM/week vs. ≤1 SBM/week, Study 201)

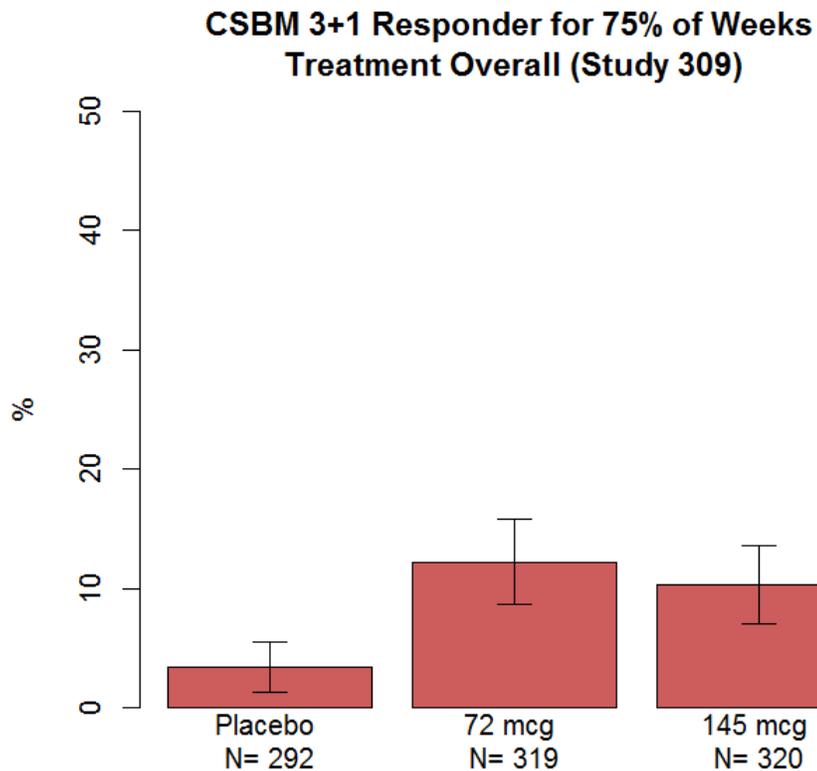


Figure 7. Dose-Response for Primary Efficacy for a Subgroup of Patients with Baseline CSBM of 0

According to the sponsor, the odds of being a 12-week CSBM Overall Responder in the 72 mcg group were reported to increase 2.7-fold in the >1 SBM/week (less symptomatic) subpopulation and 4.9-fold in the ≤ 1 SBM/week (more symptomatic) subpopulation (Sponsor’s report “MCP-103-309”, Table 14.4.2.5A). Similar analysis was conducted by the reviewer for 145 mcg dose group. The odds of being a 75% of Weeks Treatment increased 2.8-fold in the >1 SBM/week (less symptomatic) subpopulation and 3.4-fold in the ≤ 1 SBM/week (more symptomatic) subpopulation.

Recommendation

Overall, it appears that there is no meaningful effect of baseline SBM rate (>1 SBM/week and ≤ 1 SBM/week) on dose-response relationship of linaclotide in study 309. However, cross study trial comparison of 201 (baseline SBM rate=2.22 /week) and 309 (baseline SBM rate 1.65 /week) did show a different dose response relationship. It is possible that this difference is due to different treatment duration or other baseline characteristics of the treated population. Nevertheless, based

on the standalone Phase 3 study (Study 309), the proposed dose of 72 mcg QD appears to have similar effect compared to 145 mcg for the treatment of patients with CIC. This effect is consistent for both less and more symptomatic treatment population with both doses demonstrating treatment effect. Therefore, the results of study 309 support the approval 72 mcg QD for CIC.

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/s/

JEE E LEE
12/02/2016

NITIN MEHROTRA
12/02/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Medical Team Leader
John J. Alexander, MD/MPH, Deputy Director
DPMH

NDA Number: 202,811/S-010

Sponsor: Forest Laboratories, LLC

Drug: Linzess (linaclotide),

Indication: Treatment of adults with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC).

Dosage Form and Route of Administration: 72, 145, 290 mcg capsules for oral (PO) administration

Dosing regimen: IBS-C: 290 mcg PO/daily
CIC: 72 or 145 mcg PO/daily

Proposed Pediatric Regimen: None

Division Consult Request: The Division of Gastroenterology and Inborn Error Products (DGIEP) requests DPMH participation in this labeling supplement with no new pediatric information. Pediatric-related changes to labeling are restricted to moving the description of juvenile toxicity from section 13.2 (Animal Toxicology and/or Pharmacology) to section 8.4 of labeling and alternative “best word choices” pediatric language in the boxed warning and section 5 (Warnings and Precautions).

Background

On August 30, 2012, FDA approved Linzess (linaclotide), a guanylate cyclase-C agonist, for treatment of adults with irritable bowel syndrome-constipation type (IBS-C) and chronic idiopathic constipation (CIC). FDA waived pediatric study requirements for patients with CIC from birth to six months, and waived pediatric study requirements for patients with IBS-C birth to six years because there are too few patients in this age group to study (i.e., studies are impossible or highly impracticable).

There are seven current required pediatric studies addressing patients ages 7 months to 17 years for CIC and 7 years and older for IBS-C. FDA agreed to partial waiver of studies for both indications for patients younger than 2 years. Because death was seen in neonatal and juvenile mouse studies, clinical studies in patients with CIC from 6 months to 6 years will be delayed until additional nonclinical safety data are collected. The required studies under PREA are listed in Table 1 in the appendix.

Reviewer comment: The current supplement includes a new dosing regimen that triggers PREA. New PREA requirements for any outstanding studies being performed under existing PREA PMRs will need to be issued to assure completion of the PMR's if the sponsor ceases marketing of currently marketed dosing regimen.

Additionally, a proposed pediatric study request (PPSR) has been submitted and reviewed by DGIEP and DPMH that incorporates the PREA required studies, and has been determined to be generally acceptable to serve as the basis for issuance of a Written Request (NDA 202,811; review, Hausman E., May 5 2015).

DGIEP requested DPMH participation in this efficacy supplement (supplement S-010) which proposes a new dosage regimen of 72 mcg for treatment of adults with CIC. An iPSP for the new dosing regimen was submitted by the sponsor and will be reviewed separately.

The comments below are based on labeling provided to DPMH on August 31, 2016 which has undergone prior review and revision by DGIEP and pharmacotoxicology. Because linzess is approved in patients 6 years and older, pediatric labeling is distributed throughout labeling in addition to the description of pediatric clinical studies in Use in Specific Populations, Pediatric Use (8.4)

Pediatric-related labeling changes are limited predominantly to minor word choice changes (specifically: 'risk of serious dehydration' instead of '(b) (4)', 'pediatric patients less than 6 years' instead of '(b) (4)', and 'effectiveness' instead of '(b) (4)') in the description of the risk of dehydration in the boxed warning, section 5.1 (Warnings and Precautions) and 8.4 (Pediatric Use). The other substantive change to pediatric-related information is moving juvenile toxicity data from section 13.2 (Animal Toxicology and/or Pharmacology) to section 8.4 (Pediatric Use).

This review will focus on revisions to the boxed warning and the description of juvenile toxicity which has been moved from section 13.2 to section 8.4. Minor changes in word choices have been reviewed by DPMH and accepted are not highlighted in this review.

DPMH editorial suggestions are noted in **red bold italics** and deleted text is noted by ~~strikethrough~~.

Boxed Warning

Proposed

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- LINZESS is contraindicated in pediatric patients less than 6 years of age; in (b) (4) mice, (b) (4) linaclotide caused deaths due to dehydration [see Contraindications (4), (b) (4)].
- Avoid use of LINZESS in (b) (4) patients 6 years to less than (b) (4) years of age [see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].
- The safety and effectiveness of LINZESS have not been established in (b) (4) patients less than (b) (4) years of age [see Use in Specific Populations (8.4)].

Reviewer comment: Regarding the first bullet point above, per recent agreement between DPMH, Pharmacology-Toxicology, and the Labeling Development Team, descriptions of (b) (4) of labeling are now described in Pediatric Use (section 8.4).

5 Warnings and Precautions

5.1 Risk of Serious Dehydration in Pediatric Patients

Proposed

LINZESS is contraindicated in pediatric patients less than 6 years of age. The safety and effectiveness of LINZESS in pediatric patients less than (b) (4) years of age have not been established. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism resulted in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, (b) (4) 6 years of age may be more likely than older (b) (4) to develop (b) (4) diarrhea and its potentially serious consequences.

Avoid use of LINZESS in pediatric patients 6 years to less than (b) (4) years of age. Although there were no deaths in older juvenile mice, given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of LINZESS in pediatric patients 6 years to less than (b) (4) years of age [see Contraindications (4), Warnings and Precautions (5.2), (b) (4) Use in Specific Populations (8.4); (b) (4)].

Reviewer comment: The proposed edit is acceptable.

8.4 Pediatric Use

Reviewer comment: As noted above, there is no new pediatric information submitted for labeling; however the description of juvenile toxicity has been moved from section 13.2 to section 8.4. The following passage reflects changes agreed upon by DPMH, DGIEP and Pharmacology-Toxicology that enhance clinical utility of the juvenile toxicity data. These changes were most recently discussed and agreed upon at the internal labeling meeting of November 15, 2016.

LINZESS is contraindicated in (b) (4) **patients** less than 6 years of age (b) (4).
Avoid use of LINZESS in

patients 6 years to less than 18 years of *age [see Contraindications (4), Warnings and Precautions (5.1)].*

The safety and effectiveness of LINZESS in *pediatric* patients less than (b) (4) 18 years of age have not been established.

In *nonclinical studies*, deaths occurred within 24 hours in (b) (4) neonatal mice (*human age equivalent of approximately 0 to 28 days*), following oral administration of linaclotide, as described below in *Juvenile Animal Toxicity Data*. (b) (4)

Because of increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years and older to develop diarrhea and its potentially serious consequences. *LINZESS is contraindicated in patients less than 6 years of age.*

(b) (4)
Given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of LINZESS in (b) (4) patients 6 years *to less than* (b) (4) 18 years of age.

Juvenile Animal Data

In toxicology studies in neonatal *young juvenile* mice, (b) (4) oral administration of linaclotide at 10 mcg/kg/day caused deaths on post-natal day 7 (human age equivalent of approximately 0 to 28 days) (b) (4)

These deaths were due to rapid and severe dehydration produced by significant fluid shifts into the intestinal lumen resulting from GC-C agonism in (b) (4) mice. (b) (4)

~~[see Contraindications (4) and Warnings and Precautions (5.1)].~~

(b) (4) Tolerability to linaclotide increases with age in juvenile mice. In 2-week-old mice (*human age equivalent of approximately 1 to < 23 months*), linaclotide was well tolerated at a dose of 50 mcg/kg/day, but deaths occurred after a single oral dose of 100 mcg/kg. In 3-week-old mice (*human age equivalent of approximately 23 months*), linaclotide was well tolerated at 100 mcg/kg/day, but deaths occurred after a single oral dose of 600 mcg/kg. (b) (4)

Conclusion and Recommendations

The above draft labeling was negotiated between DPMH, DGIEP and other consultant divisions at the internal labeling meetings of September 1, November 1, and November 15, 2016. The reader is directed to final negotiated labeling which will reflect additional labeling not discussed in this document.

The current supplement includes a new dosing regimen that triggers PREA. New PREA requirements for any outstanding studies being performed under existing PREA PMRs will need to be issued to assure completion of the PMR's if the sponsor ceases marketing of currently marketed dosing regimen.

Appendix

Table 1: PREA Studies/Pediatric Related PMRs (adapted and updated from DPMH review, March 2016)		
PMR No.	Requirement/Commitment	Status
1915-1	A nonclinical study in neonatal and juvenile mice to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide	Fulfilled
1915-2 [^]	A safety and efficacy study in pediatric patients with chronic idiopathic constipation ages seven months up to 17 years treated with Linzess.	Released. Replaced with PMR 2161-1
1915-3	A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years up to 17 years treated with Linzess.	Pending December 2023
1915-4	Develop and validate sensitive and precise assays for the detection of anti-linaclotide antibodies, including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling.	Pending (deferral extension)
1915-5	A multiple-dose milk-only lactation trial in healthy lactating but non-nursing female volunteers receiving Linzess (linaclotide) to assess concentrations of linaclotide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Nursing Mothers' subsection of the labeling.	Released and replaced with PMR 1915-7 (see below)
1915-6	A clinical trial in adults receiving Linzess (linaclotide) to assess development of antidrug antibody (ADA) responses in patient samples. Validated assays capable of sensitively detecting ADA responses that may be present at the time of patient sampling, developed under PMR 1915-4 above, will be used. Sampling will occur at 0 and 2 weeks, and at 1, 3, 6 and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.	Pending
1915-7	A milk-only lactation trial in lactating women receiving Linzess (linaclotide) therapeutically to assess concentrations of linaclotide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Nursing Mothers' subsection of the labeling	Ongoing
2161-1*	A safety and efficacy study in pediatric patients with CIC, ages 2 to 17 years, treated with linaclotide	Pending
2825-1	A study to measure GC-C mRNA levels in duodenal and colonic tissue obtained from children ages 0 to 6 years of age	Pending
[^] Study 1915-2 originally required studies in children 7 months and older; however due to concerns with lethality in juvenile toxicity studies, this PREA study was released and replaced by Study 2161-1.		
(b) (4)		

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/s/

ETHAN D HAUSMAN
12/02/2016

HARI C SACHS
12/02/2016
I agree with these recommendations.

JOHN J ALEXANDER
12/02/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Memorandum

Date: November 22, 2016 **Date Consulted:** April 26, 2016

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: LCDR Cheronda Cherry-France, Project Manager (PM)
Division of Gastroenterology & Inborn Errors Products (DGIEP)

Drug: Linzess (linaclotide)

NDA: NDA 202811 S-010

Indication: LINZESS is a guanylate cyclase-C agonist indicated in adults for treatment of:

- Irritable bowel syndrome with constipation (IBS-C)
- Chronic idiopathic constipation (CIC)

Applicant: Forest Laboratories, LLC

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- Applicant's submitted background package for NDA 202811 Supplement #10 (S-010) submitted as SD#516 on March 25, 2016.
- Applicant's literature review, summary of pharmacovigilance database and revised label submitted as SD#570 on August 1, 2016.
- DPMH review of Trulance (plecanatide) NDA 208745. November 10, 2016. Christos Mastroyannis, M.D. DARRTS Reference ID 4011345.

Consult Question:

Review pregnancy and nursing mothers labeling.

INTRODUCTION

On April 26, 2016, DGIEP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Linzess (linaclotide) labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

On March 25, 2016, Forest Laboratories, LLC submitted an efficacy supplement, #10, to NDA 202811. The supplement proposes a new dosage regimen of 72 mcg for the treatment of adults with CIC. On June 2, 2016, the Agency advised the Applicant to provide a review and summary of all available published literature regarding linaclotide use in pregnancy and lactating women and a review and summary of relevant cases reported in their pharmacovigilance database to support the changes in the “Pregnancy” and “Lactation” sections of the labeling. On August 1, 2016, the Applicant submitted the requested information, which was found to be adequate.

Linzess (linaclotide) is a guanylate cyclase-C agonist indicated in adults for treatment of IBS-C and CIC and was approved in the U.S. on August 30, 2012.

BACKGROUND

Linaclotide and Drug Characteristics¹

LINZESS (linaclotide) is a guanylate cyclase-C (GC-C) agonist. Both linaclotide and its active metabolite (MM-419447) 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, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, linaclotide has been shown to both accelerate GI transit and reduce intestinal pain. The linaclotide-induced reduction in visceral pain in animals is thought to be mediated by increased extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves.

The molecular weight of linaclotide is \approx 1527 Daltons. Linaclotide is minimally absorbed with low systemic availability following oral administration. Concentrations of linaclotide and its active metabolite in plasma are 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

¹ LINZESS proposed package insert

calculated. No drug-drug interaction studies have been conducted with LINZESS. 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 anticipated.

The most common adverse reactions ($\geq 2\%$) reported in IBS-C or CIC patients are: diarrhea, abdominal pain, flatulence and abdominal distension.

Chronic Idiopathic Constipation

CIC, also known as functional constipation, is a common disorder, affecting between 12% and 19% of North Americans. CIC has a higher prevalence in women than in men, and the prevalence increases with age. Similar prevalences are observed in most areas worldwide.^{2,3} Prevalence rates vary depending on demographic factors and the definitions of the condition used. Actual prevalence may be greater than these estimates as not all patients seek medical attention for the condition.^{4,5} Constipation is a symptom of many diseases and is defined as infrequent stools, incomplete bowel movements (BMs), straining, bloating, and hard, lumpy stool.^{6,7}

First-line treatments for constipation currently include increased dietary fiber consumption and supplementation with bulking agents, increased exercise, increased water consumption, and bowel habit training. Often, only partial relief of symptoms is obtained with these treatments. Prescription options for the treatment of CIC in addition to linaclotide include lubiprostone (Amitiza), which activates a type-2 chloride channel in the gastrointestinal (GI) tract to increase secretion of fluid in the intestine, making it easier for a patient to have a BM.⁸

In Europe an additional drug has been approved by the European Medicines Agency (EMA), prucalopride (Resolor ^{(b) (4)}), which is a 5-hydroxytryptamine₄ receptor agonist that works as a prokinetic to target the impaired motility associated with CIC.

² Higgins, PD & Johanson, JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol.* 2004; 99:750-759.

³ Lembo A, Camilleri M. Chronic constipation. *N Engl J Med.* 2003; 349:1360-1368.

⁴ Pare P, Ferrazzi S, Thompson WG, Irvine EJ, Rance L. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. *Am J Gastroenterol.* 2001;96:3130-3137

⁵ Stewart WF, Liberman, JN, Sandler RS, et al. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. *Am J Gastroenterol.* 1999; 94:3530-3540.

⁶ Cash BD, Chang L, Sabesin SM, Vitat P. Update on the management of adults with chronic idiopathic constipation. *J Fam Practice.* 2007;96:513-519

⁷ Lembo A, Camilleri M. Chronic constipation. *N Engl J Med.* 2003;349:1360-1368

⁸ Lembo A, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (CIC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci.* 2011; 56:2639-2645.

Current State of the Labeling⁹

Current in-use labeling for LINZESS, approved on August 31, 2016, is in the Physician Labeling Rule (PLR) format but does not comply with PLLR requirements. There is a boxed warning and a contraindication for use in pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. There is also a contraindication for use in patients with known or suspected mechanical gastrointestinal obstruction and a warning for severe diarrhea. No interactions with hormonal contraceptives are noted in the 2016 label.

- LINZESS is currently labeled as a category C drug and labeling notes that “There are no adequate and well-controlled studies with LINZESS 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. LINZESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”
- Regarding lactation, current LINZESS labeling notes that “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. Caution should be exercised when LINZESS is administered to nursing women.”

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁰ also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹¹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

⁹ Linzess proposed labeling

¹⁰ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹¹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

REVIEW

PREGNANCY

Nonclinical Experience

In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of linaclotide in rats and rabbits during organogenesis at doses much higher than the maximum recommended human dosage, whereas severe maternal toxicity associated with effects on fetal morphology were observed in mice.

For further details, the reader is directed to the Nonclinical Review by David Joseph, Ph.D.

Applicant's Review of Literature

According to the Applicant,

“The Sponsor has conducted an extensive search of all common literature databases for all available published literature regarding linaclotide use in pregnant and lactating women. After reviewing the search results, there was no new information about the use of linaclotide in pregnancy or lactation.

The search strategy identified 24 non-patient records, 20 of which referred to clinical trials...14 ongoing and 6 completed. These records were identified by the search criteria due to mention of pregnancy and/or lactation in the exclusion criteria of these respective studies, not because they described cases of linaclotide use in pregnant and lactating patients. Two of the 24 records identified were journal articles which focused on lubiprostone and did not mention linaclotide use in pregnant and lactating patients. The 2 remaining records were both journal articles by the same author (Miller-Lissner) and provided a broad overview of pharmacological treatments of constipation. The only reference to linaclotide was that “no data” was available in pregnancy and lactation.”

Applicant's Pharmacovigilance Database Summary

In clinical trials, 22 patients taking linaclotide, who accidentally became pregnant, and who did not interrupt the pregnancy, were followed. Outcomes included the following:

- 3 abortions (No information on gestational age at time of abortion, dates or duration of linaclotide exposure, or presence of fetal malformations was included.)
- 19 healthy babies [of which 1 had a minor congenital malformation (polydactyly)]. The applicant did not have information regarding the dates or durations of linaclotide exposure or the gestational age of the infants at the time of birth.

In a post-approval context, 16 cases were reported of women who were exposed to linaclotide at some time during pregnancy.

- 11 unknown outcomes
 - One pregnancy with no complications up to 4 months gestation
 - One pregnancy with no complications up to 5 months gestation
 - Gestational diabetes during pregnancy, outcome unknown
- 3 live births
 - Linaclotide throughout pregnancy-healthy female infant
 - Baby with positional talipes (equino varus) but otherwise healthy
- 2 miscarriages
 - One miscarriage at \approx 8 weeks estimated gestational age (EGA)
 - No information except concomitant meds included codeine, ondansetron and Depo-Provera

DPMH’s Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms “linaclotide and pregnancy,” “linaclotide and pregnant women,” “linaclotide and pregnancy and birth defects,” “linaclotide and pregnancy and congenital malformations,” “linaclotide and pregnancy and stillbirth,” “linaclotide and spontaneous abortion” and “linaclotide and pregnancy and miscarriage.” No reports of adequate and well-controlled studies of linaclotide use in pregnant women were found. No published case reports of exposure were found.

Linaclotide is referenced in Reprotox¹² with regard to pregnancy with the following comment:

“Based on studies in rats and rabbits, linaclotide is not expected to increase the risk of congenital malformations. Mice might be more sensitive to toxic effects of this drug, but developmental effects in mice occurred only at dose levels producing severe maternal toxicity. Clinical use of linaclotide was not associated with measurable concentrations of the drug or its metabolite in the systemic circulation.”

Summary

The limited postmarketing experience with linaclotide in pregnancy is insufficient to establish the presence or absence of drug-associated risk. However, the lack of absorption suggests the risk to the fetus is minimal. DPMH recommends the following language be included in Section 8.1 Pregnancy, Risk Summary of the LINZESS labeling to summarize the data:

LINZESS is negligibly absorbed systemically following oral administration [*see Clinical Pharmacology (12.3)*], and is not expected to result in fetal exposure to the drug. The available data on LINZESS use in pregnant women are not sufficient to inform any drug-associated risk for major birth defects

¹² Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed October 18, 2016.

and miscarriage. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of linaclotide in rats and rabbits during organogenesis at doses much higher than the maximum recommended human dosage, whereas severe maternal toxicity associated with effects on fetal morphology were observed in mice.

LACTATION

Nonclinical Experience

It is not known if linaclotide is present in animal milk. No animal lactation studies have been conducted.

Juvenile toxicity studies were conducted in mice and demonstrated lethality associated with decreasing age and dose. Similar findings were seen in another drug in the class (plecanatide). DGIEP nonclinical reviewers consider that the mechanism of lethality is related to higher G-CC expression in newborn mice. Binding of an agonist to the G-CC stimulates cyclic guanosine monophosphate (cGMP) synthesis and activates CFTR which result is chloride and sodium/potassium ion efflux and secretion of fluid into the intestinal lumen. This led to dehydration and death in the youngest mice. See Table 2 below for the nonclinical reviewer’s comparison of lethal dose between plecanatide and linaclotide.

Table 1: Lethality Comparisons in Juvenile Mice between Plecanatide and Linaclotide.*

	Plecanatide		Linaclotide	
	Minimum Lethal Dose (mg/kg)	Multiples of Clinical Dose (6 mg/day) ^a	Minimum Lethal Dose (mg/kg)	Multiples of Clinical Dose (0.29 mg/day) ^b
PND 7	0.5	5X	0.05	10.4X
PND 14	10	100X	0.1	20.8X
PND 21	no deaths at up to 300	3000X	0.6	125X
PND 28	no deaths at up to 300	3000X	no deaths at up to 1	208X

* Presented at the Midcycle meeting for Trulance (plecanatide) by DGIEP Nonclinical Reviewer, Yuk-Chow Eddie Ng, Ph.D.

PND = post-natal day a: 0.1 mg/kg; b: 4.8 µg/kg

For further details, the reader is directed to the Nonclinical Review by David Joseph, PhD.

Applicant's Pharmacovigilance Database Summary/ Review of Literature

As noted under **PREGNANCY**, the Applicant conducted “an extensive search of all common literature databases for all available published literature regarding linaclotide use in pregnant and lactating women” and no relevant literature was found.

Upon approval of LINZESS in 2012, one of the Post Marketing Requirements (PMR) was for the Sponsors to conduct a clinical trial to assess if linaclotide or its active metabolite can be quantified in the breast milk of lactating women. PMR 1915-7 (formerly PMR 1915-5) was for a study entitled “An open-label, multiple-dose, milk only lactation study in lactating women receiving linaclotide therapeutically”. (b) (4)



DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*¹³, the Drugs and Lactation Database (LactMed),¹⁴ Micromedex¹⁵, and of published literature in PubMed and Embase using the search terms “linaclotide and lactation” and “linaclotide and breastfeeding.” No reports of adequate and well-controlled studies of linaclotide use in lactating women were found. No prospective lactation studies were found.

Linaclotide is referenced in LactMed¹⁴. The summary of use states:

“Linaclotide is minimally absorbed from the gastrointestinal tract and the drug and its active metabolite are not measurable in plasma following administration of recommended doses. Linaclotide would not be expected to cause any adverse effects in breastfed infants. If linaclotide is required by the mother, it is not a reason to discontinue breastfeeding.”

In *Medications and Mother's Milk*¹³, Thomas Hale, a breastfeeding expert, states the following regarding linaclotide use during lactation:

“No data - Probably Compatible...Its ability to transfer into human milk is probably low because neither the parent drug nor its metabolite are measurable in plasma following the recommended oral dose.”

¹³ Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 650-651.

¹⁴ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 8/31/16.

¹⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 8/31/16.

Micromedex¹⁵ notes that “Infant risk cannot be ruled out.”

Linaclotide is referenced in Reprotox¹² with regard to lactation with the comment

Although there were no adverse effects associated with treatment of rats during the lactation period, the sensitivity of juvenile mice to oral administration of this agent led to a contraindication in children and might prompt concern about use during lactation. Human use of linaclotide was not associated with measurable concentrations of the drug or its metabolite in blood, suggesting no opportunity for access to milk.

Summary

There are no relevant new data regarding linaclotide use in lactating women. DPMH will revise the lactation section 8.2 to be consistent with the PLLR format and will continue to include the information that linaclotide is negligibly absorbed systemically following oral administration.

USE IN FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Linaclotide is not genotoxic. Linaclotide had no effect on fertility or reproductive function in male and female rats at oral doses of up to 100,000 mcg/kg/day.

For further details, the reader is directed to the Nonclinical Review by David Joseph, PhD.

Applicant’s Review of Literature

The Applicant did not perform a search of the published literature regarding the effect of linaclotide on fertility since it was not requested by the Agency.

DPMH’s Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding linaclotide and its effects on fertility and found no relevant literature.

Summary

Animal reproductive studies of administration of linaclotide did not show any adverse effects on fertility. Since there are no human data available on the effect of linaclotide on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in linaclotide labeling.

CONCLUSIONS/RECOMMENDATIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for LINZESS (linaclotide) labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of LINZESS (linaclotide) was structured in the PLLR format to include the “Risk Summary” and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” section of LINZESS (linaclotide) labeling was formatted in the PLLR format to include the “Risk Summary” section.

DPMH Proposed LINZESS (linaclotide) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Systemic exposure to linaclotide and its active metabolite is negligible following oral administration [*see Clinical Pharmacology (12.3)*], and maternal use is not expected to result in fetal exposure to the drug. The available data on LINZESS use in pregnant women are not sufficient to inform any drug-associated risk for major birth defects and miscarriage. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of linaclotide in rats and rabbits during organogenesis at doses much higher than the maximum recommended human dosage [*see Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

The potential for linaclotide to cause harm to embryo-fetal development was studied in rats, rabbits and mice. In pregnant mice, oral dose levels of at least 40,000 mcg/kg/day given during organogenesis produced severe maternal toxicity including death, reduction of gravid uterine and fetal weights, and effects on fetal morphology. Oral doses of 5,000 mcg/kg/day, did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice. Oral administration of up to 100,000 mcg/kg/day in rats and 40,000 mcg/kg/day in rabbits during organogenesis produced no maternal toxicity and no effects on embryo-fetal development. Additionally, oral administration of up to 100,000 mcg/kg/day in rats during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation. The maximum recommended human dose is approximately 5 mcg/kg/day, based on a 60-kg body weight. Limited systemic exposure to linaclotide was achieved in animals (AUC = 40, 640, and 25 ng•hr/mL in rats, rabbits, and mice, respectively, at the highest dose levels), Linaclotide and

its active metabolite are not measurable in human plasma following administration of the recommended clinical dosages. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

8.2 Lactation

Risk Summary

There is no information regarding the presence of linaclotide in human milk, or on its effects on milk production or the breast-fed infant. Linaclotide and its active metabolite are negligibly absorbed systemically following oral administration; therefore, exposure to a breastfed infant through breastmilk is expected to be negligible [see *Clinical Pharmacology (12.3)*]. The effects of local gastrointestinal and limited systemic exposure to linaclotide on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LINZESS and any potential adverse effects on the breastfed infant from LINZESS or from the underlying maternal condition.

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/s/

JANE E LIEDTKA
11/22/2016

LYNNE P YAO
11/25/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Memorandum

Date: October 13, 2016

Reviewer(s): Lisa Harinstein, PharmD, Safety Evaluator
Division of Pharmacovigilance I (DPV-I)

Team Leader(s): Eileen Wu, PharmD, Team Leader
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Product Name(s): Linzess (linaclotide)

Subject: Ischemic colitis

Application Type/Number: NDA 202811

Applicant/Sponsor: Forest Laboratories

OSE RCM#: 2016-1933

1 INTRODUCTION

This review, conducted in response to a consultation from the Division of Gastroenterology and Inborn Errors Products (DGIEP), evaluated the FDA Adverse Event Reporting System (FAERS) database for adverse event reports of ischemic colitis with Linzess (linaclotide) to inform DGIEP as they review Efficacy Supplement (S-010) for linaclotide.

2 BACKGROUND

Linzess (linaclotide) was approved by the FDA on August 30, 2012, for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adult patients.¹ Linaclotide is a guanylate cyclase-C agonist and reduces constipation by elevating intracellular concentrations of cyclic guanosine monophosphate, thereby stimulating secretion of chloride and bicarbonate into the intestinal lumen through activation of the cystic fibrosis transmembrane conductance regulator ion channel. This results in increased intestinal fluid and accelerated transit.

During the approval program for linaclotide^{2,3}, the adverse event of ischemic colitis was considered an important safety issue because of the association of ischemic colitis with other medications indicated for treatment of IBS-C or CIC (e.g., lubiprostone, osmotic laxatives).^{4,5} The medical officer (MO) clinical reviewers evaluated three cases of ischemic colitis reported in the clinical development program.² They determined that because of issues related to the diagnosis of ischemic colitis and often transient nature of the disease, it seemed nearly impossible to retrospectively determine with any degree of certainty whether or not linaclotide caused the ischemic colitis. The MO clinical reviewers suggested the following to evaluate the causal relationship between linaclotide and the event of ischemic colitis: 1) a definitive diagnosis of ischemic colitis based on clinical evidence (such as patient reported symptoms, objective findings from clinical signs, endoscopy), 2) temporal relationship between the onset of the ischemic colitis relative to initiation of therapy and/or resolution of symptoms suggestive of ischemic colitis upon cessation of the drug, and 3) exclusion of other causes of ischemic colitis. The MO clinical reviewer of the CIC trials also identified 11 cases of interest from the CIC trials that were further evaluated for ischemic colitis. Six of 11 cases were sent for adjudication by the sponsor's Expert Panel and five were deemed not to be drug-associated by the MO clinical reviewer. The Expert Panel concluded that there was insufficient evidence to consider the six cases to represent ischemic colitis. The MO clinical reviewers ultimately determined that the available evidence did not establish a causal link between linaclotide and ischemic colitis; however, they recommended close monitoring of the safety issue in the postmarketing setting and addition of symptoms of ischemic colitis and management information to the Medication Guide for linaclotide.

Additionally, a FDAAA Section 915 New Molecular Entity Postmarket Safety Summary Analysis^a (915 Analysis) was completed on September 26, 2014 and did not identify sufficient evidence to establish a causal link between linaclotide and ischemic colitis.⁶ The 915 Analysis identified two cases of ischemic colitis in the postmarketing setting; one case did not provide

^a DPV-I searched the FAERS database for the time period of August 20, 2012 (Date of US approval of linaclotide) to February 28, 2014.

sufficient detail for causality assessment between the event of ischemic colitis and linaclotide and one case contained multiple strong alternative causes for the events of ischemic colitis and acute renal failure (see Appendix A for the two case narratives and reviewer comments reproduced from the 915 Analysis).

On March 25, 2016, DGIEP received an Efficacy Supplement (S-010) for linaclotide, which proposed a new dosage regimen of 72 mcg for the treatment of adults with CIC (current approved dosage and administration for CIC is 145 mcg once daily). At the time of the submission, the sponsor had identified four postmarketing cases of ischemic colitis in patients receiving linaclotide. Given that cases of ischemic colitis were identified as a potential signal in the original approval program and postmarketing cases of ischemic colitis were identified, DGIEP requested a formal review of all postmarketing cases contained in FAERS from the time of the completed 915 Analysis to inform DGIEP's review of the linaclotide Efficacy Supplement.⁷

The current US label for linaclotide does not contain ischemic colitis but the Medication Guide does contain information on potential signs and symptoms that may be related to ischemic colitis and management recommendations as follows:¹

In addition, call your doctor or go to the nearest hospital emergency room right away, if you develop unusual or severe stomach-area (abdomen) pain, especially if you also have bright red, bloody stools or black stools that look like tar.

3 METHODS AND MATERIALS

DPV-I searched the FAERS database with the strategy described in Table 1. The search strategy was chosen to identify all reports of ischemic colitis with linaclotide.

Date of Search	September 13, 2016
Time Period of Search	February 28, 2014 [†] - September 12, 2016
Search Type	Quick Query
Product Terms	Product active ingredient: linaclotide
MedDRA Search Term (Version 19.0)	Preferred Term (PT): Colitis ischaemic
* See Appendix B for a description of the FAERS database.	
[†] Cut-off date of FAERS search in the 915 Analysis	

4 RESULTS

The FAERS search retrieved five adverse event reports from the time of the completed 915 Analysis; two were duplicates and three were unique cases of ischemic colitis with the use of linaclotide and are described below. See Appendix C for the FAERS case numbers, FAERS version numbers, and manufacturer control numbers.

Case Summaries

Case #10668577, hospitalization, US, 2014: A physician reported that a 40-year-old female experienced bloody diarrhea and ischemic colitis requiring hospitalization 1 day after starting

linaclotide 145 mcg for an unspecified indication. Linaclotide was discontinued because of the adverse events and the outcome of the event was unknown. Relevant past medical history included anxiety, asthma, bipolar disorder, bronchitis, candida rash, dehydration, hypertension, pneumonia, and seizure disorder.

Reviewer comment: The events (bloody diarrhea, ischemic colitis) occurred 1 day after initiating linaclotide, suggesting a strong temporal relationship. Linaclotide was discontinued after the events, but the response to dechallenge was not reported. The patient had multiple comorbidities; however, concomitant medications were not provided which would be useful when assessing causality.

Case #10763934, hospitalization/ other serious important medical event, US, 2015:

A consumer reported that a 60-year-old female experienced a diverticular bleed, severe abdominal pain, nausea, and worsening constipation after starting linaclotide 145 mcg daily for treatment of IBS-C. Thirteen days after starting linaclotide, the patient was hospitalized for abdominal pain, nausea, and a diverticular bleed that did not require blood transfusion. An abdominal computed tomography (CT) scan was completed (results not reported). Linaclotide was discontinued. Four days later, the patient's abdominal pain greatly increased with localized sharp pain in the lower left quadrant. Repeat abdominal CT revealed diverticulitis per a radiologist. The next day, the patient returned to the emergency room with pain and was diagnosed with ischemic colitis. An endoscopy and colonoscopy were performed 9 days later and revealed normal results. Various diagnostic tests, such as anorectal manometry, Sitzmarks radiopaque markers, and defecography were performed, but their results were also not provided. It is unknown whether the patient received treatment medications. Approximately three months after the initial diverticular bleed, the patient underwent a laparoscopic sigmoid resection/low anterior resection and rectopexy for treatment of ongoing/restrictive constipation. At the time of this report, the patient was recovering from diverticular bleed. The outcomes of diverticulitis, ischemic colitis, and nausea were unknown. She had not yet recovered from severe abdominal pain or worsened constipation. Past medical history included chronic back pain, social alcohol consumption, and sleep apnea. Concomitant medications included intranasal fluticasone, omeprazole, montelukast, zolpidem, nabumetone, and tizanidine.

Reviewer comment: The patient initially presented with a diverticular bleed and linaclotide was discontinued at that time. The patient was diagnosed with diverticulitis 4 days later, which is a less common cause of ischemic colitis, but provides an alternative cause for the development of ischemic colitis the following day.⁸ Constipation is also associated with the development of ischemic colitis. This patient had severe constipation at the time of the diverticular bleed (ultimately requiring surgical management 3 months later for treatment of ongoing constipation), which provides another alternative cause for the event of ischemic colitis.

Case #1104660, other serious important medical event, US, 2015: A physician reported that a 43-year-old female experienced mild ischemic colitis while taking linaclotide 290 mcg for treatment of severe CIC. The patient had previously taken linaclotide 145 mcg and the dose was increased to 290 mcg daily after an unknown period of time. The event occurred approximately 11 months after starting linaclotide. Linaclotide was permanently discontinued after the event and the mild ischemic colitis resolved sometime the next month.

Reviewer comment: Information on the time between the linaclotide dose increase (145 mcg to 290 mcg) and event occurrence was not given, but would have aided in establishing whether there was a strong or weak temporal relationship between the event and linaclotide.

5 DISCUSSION

The FAERS search identified three unique cases of ischemic colitis in patients receiving linaclotide. Similar to the conclusions from the cases analyzed by the MO clinical reviewers during the clinical development program, retrospective evaluation of the FAERS cases did not provide certainty as to whether or not ischemic colitis occurs in association with linaclotide.² The one case (FAERS case #10668577) with the strongest temporal association between the event of ischemic colitis and linaclotide (event occurred 1 day after initiation) provided limited information on response to dechallenge and concomitant medications. The other two cases did not have strong temporal relationship because one case had worsening symptoms 4 days after linaclotide discontinuation and the other case developed mild ischemic colitis after 11 months of linaclotide therapy (linaclotide dose increased at unknown time relative to onset of ischemic colitis).

During the approval program for linaclotide^{2,3}, the adverse event of ischemic colitis was considered an important safety issue because of the association of ischemic colitis with other medications indicated for the treatment of IBS-C or CIC (e.g., lubiprostone, osmotic laxatives).^{4,5} Although the mechanism behind the development of ischemic colitis and these other medications has not been fully elucidated, some postulated mechanisms include production of rapid fluid shifts from the intravascular compartment of the bowel to the intestinal lumen resulting in transient colonic hypoperfusion and increased colonic motility that may cause diminished mucosal perfusion. Linaclotide has a novel mechanism of action compared to the other medications used for treatment of IBS-C and CIC that are associated with the development of ischemic colitis, but linaclotide similarly ultimately increases intestinal fluid and accelerates transit time. Therefore, it may be mechanistically possible for ischemic colitis to occur in association with linaclotide.

Although there is insufficient evidence to confirm an association between linaclotide use and ischemic colitis, a causal or contributory role of linaclotide cannot be excluded in the three identified FAERS cases. DPV-I plans to continue monitoring for reports of ischemic colitis with linaclotide.

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7 APPENDICES

7.1 APPENDIX A. TWO CASES OF ISCHEMIC COLITIS REPRODUCED FROM 915 ANALYSIS

Colitis ischaemic (PT)

- Case 9486907: A physician reported that an 85 year-old female patient experienced **ischemic colitis** after starting Linzess 145 mcg daily for treatment of constipation and abdominal pain. She was hospitalized because of the event. No additional information about the timing between initiation of drug treatment and the adverse event, medical history, concomitant drugs or outcome of the event was provided.

Reviewer comment: This case did not provide sufficient detail for causal analysis between the adverse event ischemic colitis and Linzess.

Colitis ischaemic (PT) and Renal failure acute (PT)

- Case 9867862: A physician reported that an 84-year-old female patient with multiple medical conditions including lipodermatosclerosis, atrial fibrillation, hypertension, hypothyroidism, chronic anemia, and hyperlipidemia experienced **ischemic colitis** and **acute renal failure** after starting Linzess 145 mcg daily for the treatment of chronic constipation and abdominal pain. Concomitant medications included rivaroxaban, amiodarone, prednisone, levothyroxine, hydrochlorothiazide/triamterene, methotrexate, omeprazole, vitamin D2, metoprolol, fish oil, and calcium. After starting Linzess (timing not reported), the patient began to experience weight loss (16 pounds over one month), nausea, weakness, an increase in her abdominal pain and experienced rectal bleeding. The patient was hospitalized and a colonoscopy was performed which demonstrated moderately severe ischemic colitis in the sigmoid colon, descending colon, splenic flexure, and rectosigmoid junction; the mucosa appeared edematous and erythematous. Laboratory evaluations one day after admission were notable for blood urea nitrogen (BUN) of 25 and creatinine (Cr) of 2.2; no prior laboratory data was reported. The patient recovered from the ischemic colitis and acute renal failure with rest and intravenous fluids.

Reviewer comment: Although diarrhea and admission BUN and Creatinine were not reported, the significant weight loss (16 pounds in one month) suggests that the patient may have suffered from dehydration. Dehydration may have led to acute renal failure and also ischemic colitis. Concomitant use of hydrochlorothiazide/triamterene may have also contributed to the development of acute renal failure.

7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic

products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

FAERS Case Numbers	FAERS Version Numbers	Manufacturer Control Numbers
10668577	1	US-FRI-1000073030
10763934	1	US-FRI-1000074174
11104660	1	US-FRI-1000076326

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/s/

LISA M HARINSTEIN
10/13/2016

EILEEN WU
10/13/2016

CINDY M KORTEPETER
10/13/2016

ROBERT L LEVIN
10/13/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 7, 2016
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 202811/S-010
Product Name and Strength:	Linzess (linaclotide) capsules 72 mcg (proposed), 145 mcg, 290 mcg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Forest Laboratories, LLC and Ironwood Pharmaceuticals, Inc.
Submission Date:	March 25, 2016
OSE RCM #:	2016-845
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Linzess (NDA 202811/S-010), submitted on March 16, 2016 as an Efficacy Supplement. This supplement proposes an additional 72 mcg strength for the treatment of adult patients with chronic idiopathic constipation (CIC). The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information, carton labeling, and container labels for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Forest Laboratories, LLC and Ironwood Pharmaceuticals, Inc. submitted an efficacy supplement which proposes a new strength of 72 mcg. Linzess is currently available in strengths of 145 mcg and 290 mcg capsules. The current recommended dosage for the treatment of adult patients with chronic idiopathic constipation (CIC) is 145 mcg daily and the recommended dosage for the treatment of irritable bowel syndrome with constipation (IBS-C) is 290 mcg daily. This supplement proposes a dosage of 72 mcg daily for CIC patients depending on individual clinical presentation or response to the starting dose. We evaluated the introduction of the proposed 72 mcg strength and find it to be appropriate for the dosing regimen. Our search of the ISMP Newsletters did not identify any medication errors relevant to the labels and labeling of Linzess. Additionally, we reviewed the container labels and carton labeling for all three strengths to ensure that they are well differentiated to mitigate the risk of wrong strength errors. We note

that the (b) (4) 72 mcg strength (b) (4) and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength errors.

Therefore, we find the addition of the 72 mcg strength and the proposed Prescribing Information acceptable from a medication error perspective. However, the proposed carton labeling and container label can be improved to ensure adequate differentiation between the strengths. We provide letter-ready recommendations for the Applicant in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

We find the addition of the 72 mcg strength and the proposed Prescribing Information acceptable from a medication error perspective. However, the proposed carton labeling and container label can be improved to mitigate the risk of wrong strength errors.

4.1 RECOMMENDATIONS FOR FOREST LABORATORIES, LLC AND IRONWOOD PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this Supplement:

- A. Revise (b) (4)
The use of (b) (4) one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Linzess that Forest Laboratories, LLC and Ironwood Pharmaceuticals, Inc. submitted on March 25, 2016.

Table 2. Relevant Product Information for Linzess	
Initial Approval Date	August 30, 2012
Active Ingredient	Linacotide
Indication	Treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC)
Route of Administration	Oral
Dosage Form	Capsules
Strength	72 mcg (proposed), 145 mcg, 290 mcg
Dose and Frequency	IBS-C: 290 mcg orally once daily CIC: 72 mcg or 145 mcg orally once daily
How Supplied	Trade bottle containing 30 capsules of 72 mcg, 145 mcg or 290 mcg
Storage	25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)[see USP Controlled Room Temperature]
Container Closure	HDPE bottles (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 4, 2016, we searched the L:drive and AIMS using the terms, Linzess to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews^{a,b,c} and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On October 4, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Linzess

D.2 Results

We did not identify any articles associated with medication errors or relevant to the labels and labeling for Linzess.

^a Abraham, S. Label and Labeling Review for Linzess (NDA 202811). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 09 01. 32 p. OSE RCM No.: 2015-1846.

^b Khosla, L. Label and Labeling Review for Linzess (NDA 202811). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 07 15. 32 p. OSE RCM No.: 2013-1299.

^c Wilker Parker, J. Label and Labeling Review for Linzess (NDA 202811). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 02 15. 32 p. OSE RCM No.: 2011-3178.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Linzess labels and labeling submitted by Forest Laboratories, LLC and Ironwood Pharmaceuticals, Inc. on March 25, 2016.

- Container label
- Carton labeling
- Sample container label
- Sample carton labeling
- Prescribing Information

G.2 Label and Labeling Images

Container labels

Proposed strength:

(b) (4)



Currently approved strengths:

^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERLY ABRAHAM
10/07/2016

MISHALE P MISTRY
10/12/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s010

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 63290

MEETING MINUTES

Ironwood Pharmaceuticals, Inc.
Attention: Chrissy Pierce, M.S.
Director, Regulatory Affairs
301 Binney Street
Cambridge, MA 02142

Dear Ms. Pierce:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for linaclotide.

We also refer to the meeting between representatives of your firm and the FDA on September 9, 2014. The purpose of the meeting was to discuss your proposed Phase 3 clinical trial (MCP-103-309).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

CDR Matthew Brancazio, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: September 9, 2014 at 10:00-11:00 am EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: IND 63290
Product Name: Linaclotide
Indication: **Linaclotide is indicated in adults for the treatment of chronic idiopathic constipation (CIC)**
Sponsor/Applicant Name: Ironwood Pharmaceutical, Inc.

Meeting Chair: Robert Fiorentino
Meeting Recorder: Matthew Brancazio

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Andrew E. Mulberg, M.D., F.A.A.P, Deputy Director, Division of Gastroenterology and Inborn Errors Products
Robert Fiorentino, M.D., M.P.H., Medical Team Leader, Division of Gastroenterology and Inborn Errors Products
Farrokh Sohrabi, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products
Wen Jen Chen, Ph.D., Statistical Reviewer, Division of Biometrics III
Mike Welch, Ph.D., Deputy Director, Division of Biometrics III
CDR Matt Brancazio, Pharm.D., Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Product

SPONSOR ATTENDEES

Ironwood Pharmaceuticals

Michael Hall, M.D., Senior Vice President, Clinical Development
Caroline Kurtz, Ph.D., Vice President, GC-C Platform Lead
Joe Lavins, M.D., Senior Director, Clinical Research
Chrissy Pierce, M.S., Director, Regulatory Affairs
David Reasner, Ph.D., Vice President, Data Science
Gwyn Reis, Vice President, Regulatory Affairs

Forest Laboratories

Rick Blakesley, Ph.D., Associate Director, Statistical Science
Linda Kunka, M.A., Associate Director, Regulatory Affairs
Daniel Jia, Ph.D., Senior Director, Biostatistics
Steven Shiff, M.D., Executive Director, Clinical Development

1.0 BACKGROUND

Linzess is indicated for the treatment of Irritable Bowel Syndrome with constipation (IBS-C) and Chronic Idiopathic Constipation (CIC) in adults and was originally approved by the Division on August 30, 2012. On June 26, 2014, Ironwood Pharmaceuticals requested, and was granted, a type C meeting with the Division of Gastroenterology and Inborn Errors Products (DGIEP). This meeting between Ironwood Pharmaceuticals, Inc. and DGIEP is for Ironwood Pharmaceuticals, Inc. to obtain the Division's feedback and agreement that the single proposed Phase 3 clinical trial (MCP-103-309), as designed, is adequate, in combination with supportive data previously obtained from the Phase 2b Study MCP-103-201, and the Phase 3 registration trials, to base the approval of a lower dose of Linzess (72 ug).

2.0 DISCUSSION

2.1. Clinical and Statistical

Question 1: *We plan to conduct a single adequate and well-controlled 12-week efficacy trial to confirm that 72 ug of Linzess is an effective dose in patients with CIC. To support the indication that "Linzess is indicated for the treatment of CIC in adults," we have selected overall complete spontaneous bowel movement (CSBM) response as the primary endpoint. (A CSBM overall responder is a patient who meets the criteria of being a CSBM weekly responder for 9 out of the 12 treatment weeks. A CSBM weekly responder is a patient who has a CSBM frequency during the treatment week that is at least 3 CSBMs/week and increases by at least 1CSBM/week from Pre-Treatment.) Hypothesis testing for the 72 ug Linzess arm will be conducted employing a four-step serial-gatekeeping procedure (SGP). If all the individual hypotheses within a step are statistically significant (nominal $\alpha=0.05$) then the SGP moves to the next step by a single branch. Otherwise, if all individual hypotheses within a step are not rejected, the hypothesis tests in the current step as well as subsequent steps will be considered not statistically significant. If the procedure reaches the last step, a stepwise multiple comparison method will be employed to control the Type I error rate (see study synopsis for additional details on the SGP and multiple comparison method). In particular,*

- *Step 1 will test the primary efficacy parameter in the overall population*
- *Step 2 will test the primary efficacy parameter in a pre-specified stratum defined as those patients reporting greater than 1 SBM per week during the Pre-Treatment period*
- *Step 3 will test three secondary efficacy parameters*
- *Step 4 will test three additional secondary efficacy parameters*

a. Does DGIEP agree with the proposed primary and secondary endpoints as detailed in the MCP-103-309 draft protocol synopsis?

b. Does DGIEP agree that the design of MCP-103-309 could support the addition of the proposed 72 ug dose level to the Linzess label?

c. Does DGIEP have any specific comments related to the design of the proposed trial?

FDA Response to Question 1:

1a: No, we do not agree. It is important to patients and healthcare providers that durability of response is established, particularly for a lower dose of Linzess. Accordingly, the Division recommends adding to the responder definition the criterion that out of the 9 weeks of weekly CSBM response, at least 3 weeks should occur in the last 4 weeks of the 12-week treatment period.

Regarding the proposed secondary endpoints, we have the following comments/recommendations:

- Secondary analyses of monthly responders for each month (e.g., responder for 3 out of 4 weeks) should also be presented.
- The content validity of the scales used to assess straining, abdominal discomfort, and abdominal bloating have not been validated as a Patient Report Outcome measure; however, we acknowledge that FDA review of the acceptability of such endpoints is ongoing.
- We also note that under step 3 and step 4, there are multiple endpoints being tested and the multiplicity adjustment approach is not well described. Your statistical analysis plan should clearly detail your approach to multiplicity adjustment.

Your protocol and statistical analysis plan should provide details on how missing data will be handled for the primary endpoint and secondary endpoints.

1b: See our responses to question #1a and question 4, and FDA additional comments.

1c: See our responses to question #1a and question 4, and FDA additional comments. The Division may have additional specific comments once you have submitted a complete protocol and statistical analysis plan to the Division for review.

Meeting Discussion:

The sponsor proposes and maintains their original plan to use the original phase 3 primary endpoint as the primary endpoint as well as to include the monthly responder analysis to assess the durability of response as a secondary analysis. The FDA's recommended primary endpoint would be conducted as a sensitivity analysis. The sponsor understands that this is a review issue and will have labeling and approvability implications.

Question 2: *Does DGIEP agree with the planned safety measures in the proposed trial?*

FDA Response to Question 2:

In your protocol synopsis, you have noted the following planned safety measures:

AE recording (each visit), clinical laboratory measures (chemistry and hematology: Screening, Randomization, and End-of-Treatment Period Visits; urinalysis not obtained), vital sign parameters (each visit); ECGs not obtained, diarrhea questionnaire (Week 2, 4, and 8 Visits and End-of-Treatment Period Visit limited to patients who report an AE consistent with the MedDRA preferred term of diarrhea).

Although your proposed safety measures appear generally acceptable, we cannot agree with the planned safety measures until you have submitted a complete protocol to the Division for review and comment.

Meeting Discussion:

No discussion noted.

2.2. Regulatory

Question 3: *As recommended in the FDA's March 2007 Guidance on Target Product Profile — A Strategic Development Process Tool, the Sponsors have specified labeling concepts that are in line with the goals of developing and obtaining approval for a lower dose of Linzess.*

Does DGIEP agree that MCP-103-309, as designed, and if the data are favorable, supports the labeling concepts proposed in the TPP (specifically the Dosage and Administration and Adverse Reactions sections)?

FDA Response to Question 3:

It is premature to provide definitive commentary on proposed labeling; however we note that in the *Dosage and Administration* section of the PI, you propose to add that (b) (4)

Although “(b) (4)” are defined and assessed in a clinical trial setting, in clinical practice patients with CIC are likely to be using laxatives *as needed*. Therefore, unless you can provide suitable evidence to the contrary, patient recall of the number of weekly “(b) (4)” bowel movements seems unreliable in clinical practice.

Meeting Discussion:

The sponsor proposed addressing the agency's concern with a proposed altering of the labeling text to “(b) (4)”

The sponsor indicated that this may make more sense from a clinical practice perspective.

Question 4: *The May 1998 FDA Guidance Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products allows, under certain circumstances, for effectiveness of “different doses, regimens, or dosage forms” to be determined by Extrapolation from Existing Studies, or by conducting a Single Study of a New Use, with Independent Substantiation From Related Study Data. Since Linzess and its active metabolite are minimally absorbed with low systemic availability following oral administration, extrapolation on the basis of pharmacokinetics is not possible for our product as the relationship between blood concentration and response is not possible. The guidance goes on to say that in these circumstances where the relationship between blood concentration and response is not so well understood, a single additional efficacy study should ordinarily be sufficient. The proposed 72ug dose has been studied in our Phase 2 study (Study No. MCP-103-201) and results suggest that the dose was effective.*

Does DGIEP agree with our interpretation of the FDA Guidance that one adequate and well-controlled Phase 3 trial (as proposed in this briefing book; MCP-103-309), as well as the supportive data from the pivotal Phase 3 CIC trials and the Phase 2b MCP-103-201 study, are sufficient to support approval of the 72 ug dose of Linzess?

FDA Response to Question 4:

A single additional adequate and well-controlled clinical trial could be sufficient to support submission of a supplemental NDA for the 72 mcg dose of Linzess for the treatment of CIC in adults. However, whether this single additional trial will provide substantial evidence of efficacy to support approval of the 72 mcg dose of Linzess for the treatment of CIC in adults will be a review issue.

FDA Additional Comments:

- Consider designing the trial to evaluate efficacy of a higher dose (145 mcg) in patients who do not respond to the 72 mcg dose (e.g., after ≥ 4 failed weeks). Similarly, the trial could explore dose reduction in those patients who have diarrhea on the 145 mcg dose.
- Please provide a status update on pediatric program for Linzess in CIC.

Meeting Discussion:
No discussion noted.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that

you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

At the end of the meeting, no issues required further discussion.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW B BRANCAZIO
09/09/2014